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(54) Title: PIPERIDINE DERIVATIVES AS SUBTYPE SELECTIVE N-METHYL-D-ASPARTATE ANTAGONISTS

(57) Abstract: Described are piperlines of Formula (I) and pharmaceutically acceptable salts thereof. The compounds of Formula (I) are antagonists of NMDA receptor channel complexes useful for treating cerebral vascular disorders such as, for example, stroke, cerebral ischemia, central nervous system disorders, depression, trauma, hypoglycemia, neurodegenerative disorders, anxiety, migraine headache, convulsions, Parkinson's disease, aminoglycoside antibiotics-induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal, pain, especially chronic pain, neuropathic pain, or surgical pain, or urinary incontinence.



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PIPERIDINE DERIVATIVES AS SUBTYPE SELECTIVE N-METHYL-D- ASPARTATE ANTAGONISTS

FIELD OF INVENTION

The invention relates to piperidine derivatives as N-Methyl-D-Aspartate
5 (NMDA) antagonists useful in the treatment of diseases and disorders responsive
to antagonism of NMDA receptors.

BACKGROUND OF THE INVENTION

Many of the physiological and pathophysiological effects of the
endogenous excitatory neurotransmitter glutamate are mediated via actions at
10 N-Methyl-D-Aspartate (NMDA) receptors. Over-excitation of the NMDA
receptors on postsynaptic cells-mediated by excessive release of glutamate from
nerve endings or glial cells-results in a massive calcium ion influx through a
calcium ion channel into neuronal cells, leading to neuronal cell death. These
events occur under ischemic or hypoxic conditions such as, for example, stroke,
15 hypoglycemia, cardiac arrest, or acute physical trauma.

NMDA receptors *in vivo* form an NMDA receptor channel complex in cell
walls comprising at least three binding domains, including a glutamic acid (or
NMDA) recognition site, a channel blocking binding site, and a strychnine-
insensitive glycine binding site. Physiologically, a blockade of at least one of these
20 sites terminates the channel opening of the NMDA receptor, thereby preventing
calcium ion influx into cells. Accordingly, an NMDA receptor antagonist is
therapeutically useful because it minimizes damage to the central nervous system
induced by calcium ion influx under ischemic or hypoxic conditions.

A functional NMDA receptor is comprised of the combination of at least
25 one subunit termed "NR1", which has 8 splice variants including NR1A, and one
(or more) subunit termed "NR2A", "NR2B", "NR2C", and "NR2D". The
combinations are designated NR1/2A, NR1/2B, NR1/2C and NR1/2D,
respectively. The different NR2 subunits have distinct developmental and

anatomical distributions. This suggests that agents that selectively antagonize one NR1/NR2 combination would have therapeutic actions without the psychotomimetic or dysphoric side effects associated with antagonists which block multiple NR1/NR2 combinations.

5 A subtype-selective NMDA receptor antagonist may be identified by methods well known in the pharmaceutical arts, such as, for example, screening compounds in an electrophysiology assay. In one such electrophysiology assay, different subunit combinations of recombinant NR1 and NR2 receptors are expressed in *Xenopus* oocytes, and a potential agent is administered at different
10 concentrations. NMDA-based electrical currents are activated by co-administration of fixed concentrations of an excitatory amino acid such as, for example, glutamic acid or glycine. The ability of an agent to antagonize the activation of the electrical current by an excitatory amino acid is measured by recording the change in the current versus the change in the concentration of the
15 agent.

Screening of compounds in recent years have identified a number of NMDA receptor antagonists that have been used in animal and clinical human studies to demonstrate proof of concept for use of such an antagonist in the treatment of a variety of disorders. Disorders known to be responsive to blockade
20 of NMDA receptors include acute cerebral ischemia (stroke or cerebral trauma, for example), muscular spasm, convulsive disorders, pain, including chronic and neuropathic pain, anxiety, and chronic neurodegenerative disorders such as Parkinson's disease. NMDA receptor antagonists may also be used to prevent tolerance to opiate analgesia or to help control symptoms of withdrawal from
25 addictive drugs. In fact, excessive excitation by neurotransmitters may be responsible for the loss of neurons in a wide variety of conditions. Additional conditions include cerebral vascular disorders such as cerebral ischemia or cerebral infarction resulting in a range of conditions such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, hypoglycemia, cardiac arrest, status
30 epilepticus, perinatal, asphyxia anoxia, such as from near drowning, pulmonary surgery and cerebral trauma, as well as lathyrism, Alzheimer's disease, and Huntington's disease. Other conditions amendable to treatment with an subtype-

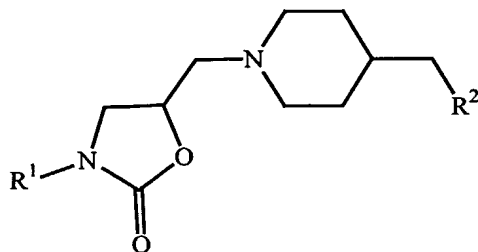
selective NMDA receptor antagonist include amyotrophic lateral sclerosis (ALS), epilepsy, and schizophrenia.

For example, studies have demonstrated that compounds that act as antagonists at NMDA receptors have beneficial pharmacological effects on patients suffering from Parkinson's disease. In Parkinson's disease, there is a loss of dopamine neurons in the substantia nigra. Secondary to this dopamine loss is a hyperactivity of specific brain glutamatergic pathways. This glutamatergic hyperactivity is thought to mediate some of the pathophysiological aspects of Parkinson's disease, as well as some of the side effects associated with the long term treatment of the disease by dopamine agonists, such as L-DOPA, pergolide, ropinirole or pramipexole. Clinical studies in humans have demonstrated that antagonists at NMDA receptors have beneficial effects in Parkinson's disease or in treating the side effects associated with the treatment of Parkinson's disease with dopamine agonists.

Pain is another example of a condition shown to be responsive to NMDA receptor antagonism. For example in previous studies, stimulation of NMDA receptors by afferent nerves transmitting painful stimuli has been demonstrated to be involved in hyperalgesic and neuropathic pain states. Animal studies have demonstrated that compounds that act as antagonists at NMDA receptors have beneficial effects in treating hyperalgesic and neuropathic pain states.

However, while NMDA antagonists have been successfully used to demonstrate the proof of concept mentioned above, very few, if any, of these antagonists have shown a suitable drug profile in clinical studies. This is so even though numerous NMDA receptor antagonists have been synthesized and tested. For example, U.S. Patent Nos. 5,714,502; 6,124,317; 6,124,323; and 6,130,234 describes the piperidine-based NMDA receptor antagonists shown below.

U.S. Patent No. 5,714,502 provides piperidines of formula



in which

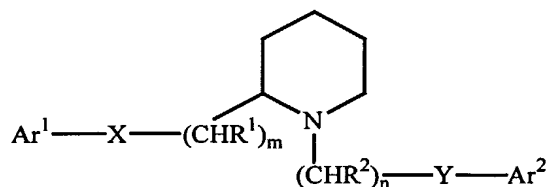
- R^1 and R^2 in each case independently of one another are unsubstituted or mono- to disubstituted phenyl radicals whose substituents can be A, OA, aryloxy having 6 to 10 C atoms, aralkyloxy having 7 to 11 C atoms, $-O-(CH_2)_n-O-$ (bonded in directly adjacent positions or in the meta- or para-position to one another on the phenyl ring), $-O-(CH_2)_n-OH$, Hal, CF_3 , OH, NO_2 , NH_2 , NHA, NA_2 , NHR^3 , NAR^3 , SO_2NH_2 , SO_2NHA , SO_2NA_2 , SO_2NHR^3 (excluding $R^3=SO_2A$), $SO_2N(R^3)_2$ (excluding $R^3=SO_2A$) or R^3 ,
- 10 R^3 is COH, CO-alkyl having 1 to 7 C atoms in the alkyl portion, CO-alkyl-aryl having 8 to 12 C atoms in the alkyl and aryl portions, CO-aryl having 7 to 13 C atoms in the aryl portion, or SO_2A

A is an alkyl radical having 1 to 6 C atoms

n is 1 or 2

- 15 Hal is F, Cl, Br, or I,
and their physiologically acceptable salts. The invention also relates to the preparation of these novel compounds and their use as psychopharmacologically active substances.

- U.S. Patent No. 6,124,317 provides 2-substituted piperidine NMDA
20 receptor antagonists of formula



or a pharmaceutically acceptable salt thereof wherein

- Ar^1 and Ar^2 are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, a halogenated alkyl group, halogen, nitro, aryl, aralkyl, amino, a lower alkyl amino group or a lower alkoxy group;
- 25 each R^1 is independently hydrogen, alkyl or hydroxy;

each R^2 is independently hydrogen, alkyl or hydroxy;

X is $-\text{CH}_2-$, O, S, or NR^3 , wherein R^3 is hydrogen or a lower alkyl group having 1 to 6 carbon atoms;

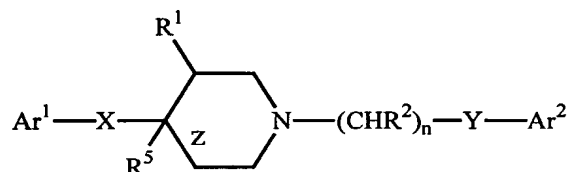
Y is $-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, O, S or NR^3 ;

5 m is 0, 1 or 2; and

n is 0, 1, 2, 3, 4 or 5,

provided that when m is 0 and X is $-\text{CH}_2-$, or m is 1, R^1 is H and X is $-\text{CH}_2-$ that either Y is not $-\text{CH}_2-$ or at least one of R^2 is not hydrogen and further provided that when Y is $-\text{C}=\text{C}-$ then X is not O.

10 U.S. Patent No. 6,124,323 provides 4-substituted piperidine-based NMDA receptor antagonists of formula



or a pharmaceutically acceptable salt thereof wherein

15 Ar^1 and Ar^2 are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, cyano, carboxaldehyde, aldehyde oxime, lower alkoxy carbonylmethyl, hydroxy lower alkyl, amino carbonylmethyl, hydrazinocarbonylmethyl, acetamido, aryl, aralkyl, amino, a halogenated alkyl group, a lower alkyl amino group or a lower alkoxy group;

20 z is a single or double bond;

X is $-(\text{CHR}^3)_m-$, O, S or NR^4 , wherein each R^3 is independently hydrogen, hydroxy or a lower alkyl group having 1 to 6 carbon atoms, R^4 is hydrogen or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, provided that when z is a double bond then X is not O or NR^4 ;

25 R^1 is hydrogen or hydroxy;

each R^2 is independently hydrogen, hydroxy or a lower alkyl group having 1 to 6 carbon atoms;

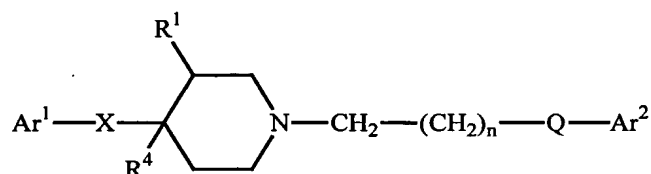
n is 0, 1, 2, 3 or 4;

Y is O, S, NR⁴ or a single bond; and

R⁵ is hydrogen or hydroxy when z is a single bond preferably provided that:

- (i) R² cannot be hydroxy in a position alpha to Ar²; (ii) if X is a single bond, z is a double bond or R⁵ is hydroxy and Ar² is phenyl then Y cannot be O; (iii) if Y is O, n is 3 or 4, R² is exclusively hydrogen, z is a single bond, R¹ and R⁵ are hydrogen and Ar² is phenyl, or halogen, methoxy, or trifluoromethyl substituted phenyl then X cannot be methylene or ethylene; (iv) if X is -(CHR³)_m, m is 2 and R³ is exclusively hydrogen then Ar¹ cannot be imidazolyl substituted; (v) if Y is O, n is 2, 3 or 4, R² is hydrogen or hydroxy, z is a single bond, R¹ and R⁵ are hydrogen, and Ar² is phenyl, or NO₂, CN, 1-imidazolyl, or 1,2,4-triazol-1-yl substituted phenyl then X cannot be methylene, hydroxymethylene, or O; (vi) if Y is O or S, R¹ and R⁵ are hydrogen and R² is hydroxy then X is not methylene or a single bond; or (vii) if Y is a single bond, R² is exclusively hydrogen and Ar² is phenyl, then either R¹ or R⁵ must be hydroxy.

U.S. Patent No. 6,130,234 provides piperidine-based NMDA receptor antagonists of formula



or a pharmaceutically acceptable salt thereof wherein

- Ar¹ and Ar² are independently aryl or a heteroaryl group, either of which may be independently substituted by hydrogen, hydroxy, alkyl, halogen, nitro, aryl, aralkyl, amino, a halogenated alkyl group, -NHAc, -NHSO₂Me, -N(SO₂Me)₂, -CONHalkyl, -SO₂NH₂, an alkylguanidine group, a lower alkyl amino group or a lower alkoxy group;
- z is a single or double bond;

X is $-(\text{CHR}^2)_m-$, O, S or NR^3 , wherein each R^2 is independently hydrogen, hydroxy, lower alkoxy or a lower alkyl group having 1 to 6 carbon atoms and m is 0, 1 or 2, and R^3 is hydrogen or a lower alkyl group having 1 to 6 carbon atoms, provided that when z is a double bond then X is not O, S or NR^3 ;

R^1 is hydrogen or hydroxy;

n is 0, 1 or 2;

Q is $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$; and

R^4 is hydrogen or hydroxy when z is a single bond provided that: (i) when n is 0,

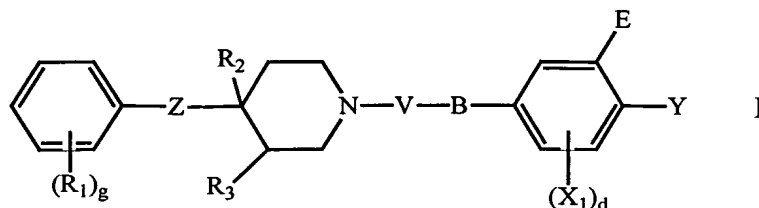
then z is a double bond and R^4 is not present; (ii) when n is 1 or 2 and Q is $-\text{C}\equiv\text{C}-$ and z is a double bond or R^4 is hydroxy, then Ar^1 is aryl substituted by halogen; and (iii) when R^4 is hydroxy then R^2 is not hydroxy or lower alkoxy.

The difficulty referenced above with demonstrating clinical utility of NMDA receptor antagonists has been the antagonists' lack of NMDA receptor subtype selectivity and/or biological activity when dosed orally. Before the present invention, many of the drugs of the NMDA receptor antagonist class were nonselective antagonists of NMDA receptor subtypes that were administered intravenously (IV), which accounts for their undesired side effects and lack of efficacy, respectively. Given that the need for medicinal agents that treat diseases responsive to antagonism of NMDA receptors remains unmet, the search for NMDA receptor antagonists that are subtype-selective and orally efficacious continues.

A series of novel piperidines have been discovered that are subtype-selective NMDA receptor antagonists and are efficacious *in vivo* when dosed orally. All that is needed to practice the invention is to administer from 1 to 6 times daily to a patient in need thereof, a therapeutically effective amount of a compound of the invention. As is discussed below, determination of dosage forms and amounts of the invention compounds, routes of administration, and identification of patients in need of treatment, is within the average skill in the pharmaceutical and medical arts.

SUMMARY OF THE INVENTION

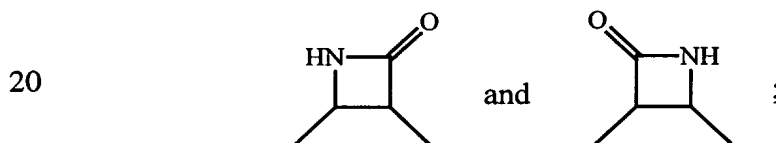
Described are piperidines of Formula I



and pharmaceutically acceptable salts thereof wherein:

- 5 R_1 is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkylaminoalkyl, hydroxyalkyl, (aminocarbonyl)-alkyl, (alkylthio)-alkyl, carboxyalkyl, haloalkyl, and halogen;
- g is an integer of from 0 to 3;
- 10 Z is $(CH_2)_h$, $C=O$, O , S , SO , SO_2 , $CHOH$, or $C(Me)OH$;
- h is an integer of from 0 or 1;
- R_2 is hydrogen, OH , alkoxy, or substituted alkoxy;
- R_3 is hydrogen, OH , alkoxy, or substituted alkoxy;
- V is $(CH_2)_n$ or $(CH_2)_m-C=O$, wherein n is an integer of from 1 to 4, and m is an
- 15 integer of from 0 to 4;
- B is a 4-, 5-, or 6-membered, carbon-linked, substituted or unsubstituted, heterocyclene, containing from 1 to 3 heteroatoms, which are N , O , or S , selected from the group consisting of:

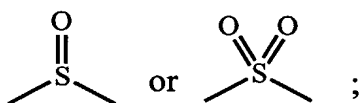
- (i) 1-aza-2-cyclobutanon-3,4-diyl of formula



- (ii) a 5-membered aromatic, nonaromatic dihydro, or nonaromatic tetrahydro diradical heterocyclic ring having carbon atoms and from 1 to 3 heteroatoms selected from N , O , and S ;

- (iii) a 5-membered oxo-substituted, nonaromatic tetrahydro, diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms selected from N, O, and S;
- (iv) a 6-membered aromatic, nonaromatic tetrahydro, or nonaromatic hexahydro diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms, which heteroatoms are nitrogen, and
- (v) a 6-membered nonaromatic oxo-substituted hexahydro diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms which are nitrogen and 0 or 1 heteroatom which is oxygen

wherein the atoms of the heterocyclene ring that are bonded to the group V and the phenyl bearing the group $(X_1)_d$ are carbon atoms, and further wherein when B is a nonaromatic heterocycle containing sulfur, said sulfur may further comprise



X_1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, aralkyl, substituted aralkyl, halogen, haloalkyl, cyano, nitro, amino, aminoalkyl, alkylaminoalkyl, hydroxyalkyl, carboxyalkyl, (aminocarbonyl)-alkyl, (alkylthio)-alkyl, or C(O)-alkyl;

d is an integer of from 0 to 2;

E is hydrogen; and

Y is OH; or

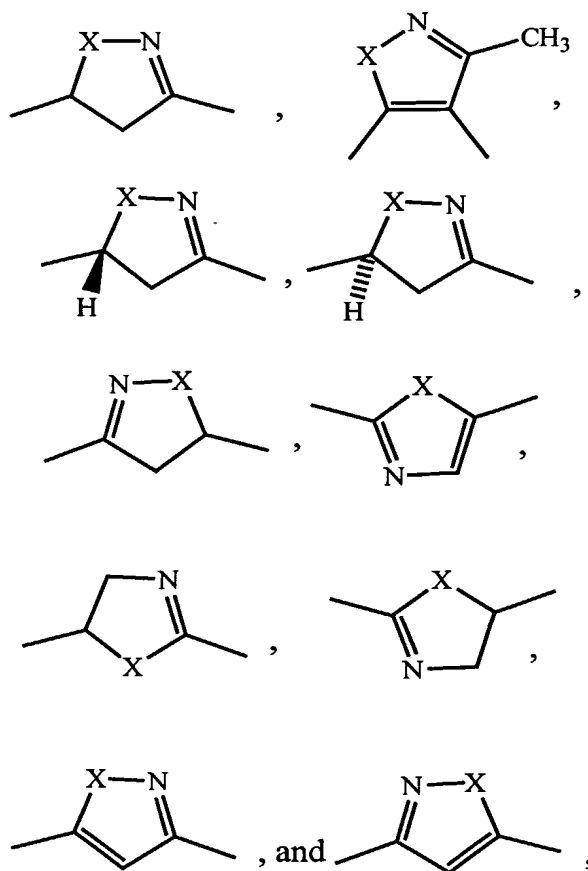
E and Y may be taken together with the phenylene to which they are attached to form a fused 9- or 10-membered bicyclic ring, containing from 0 to 3 heteroatoms in E to Y selected from N, O, and S, wherein

E is a linker group containing 2 or 3 atoms of the bicyclic ring, and
Y is a hydrogen bond donor group containing 1 atom of the bicyclic ring.

Preferred is a compound of Formula I wherein:

B is a heterocyclene selected from the group consisting of:

10



wherein X is selected from O, S, and N-R, wherein R is hydrogen or alkyl;

X₁ is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted

alkoxy, aralkyl, halogen, haloalkyl, cyano, nitro, amino, aminoalkyl,

5 alkylaminoalkyl, hydroxyalkyl, carboxyalkyl, (aminocarbonyl)-alkyl,

(alkylthio)-alkyl, or C(O)CH₃, and one X₁ is ortho to V and para to E; and

R₂ is hydrogen or OH;

R₃ is hydrogen or OH;

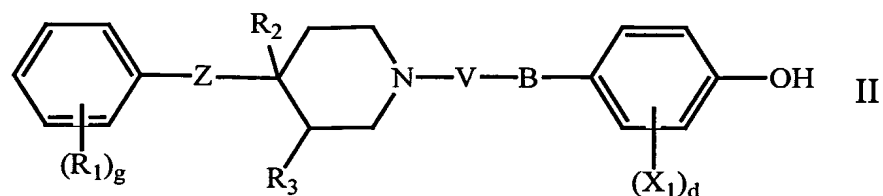
V is CH₂ or C=O;

10 Z is (CH₂)_h; and

h is 1.

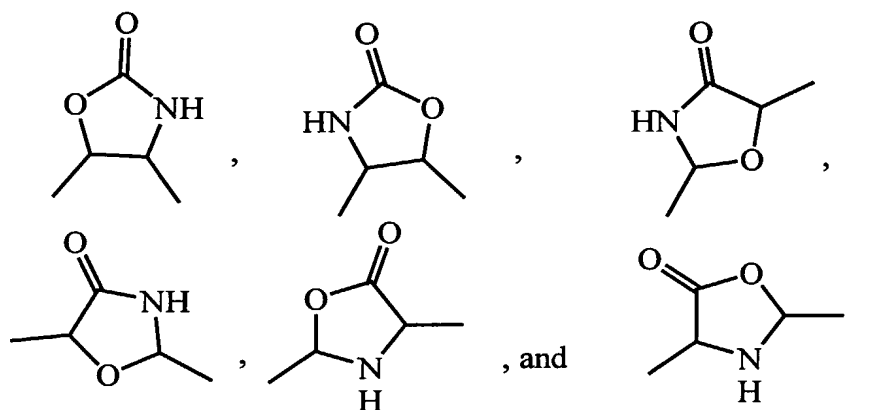
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Preferred is a compound of Formula II

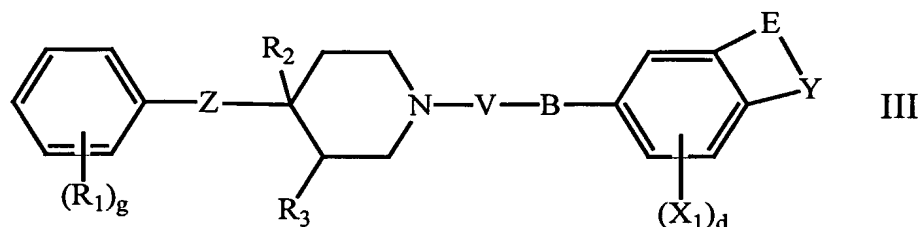


and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , B , X_1 , and d are as defined above for Formula I; and wherein when B is a

- 5 5-membered, oxo-substituted, nonaromatic tetrahydro, diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms selected from N, O, and S which is an oxazolidinone, the oxazolidinone is selected from:



Also preferred is a compound of Formula III



and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , B , X_1 , and d are as defined above for Formula I; and

E and Y together with the phenylene to which they are attached form a 9- or
10-membered bicyclic ring, containing from 0 to 3 heteroatoms selected
from N, O, and S wherein

E is a linker group containing 2 or 3 atoms of the bicyclic ring; and
Y is a hydrogen bond donor group containing 1 atom of the bicyclic
ring.

More preferred is a compound of Formula III wherein

Y is selected from -N(H)-, -CH(OH)-, and -N(OH)-, and

E is selected from -CH=CH-, -CH₂-CH₂-, -CH=N-, -C(O)-CH₂-, -CH₂-C(O)-,
 -CH₂-S(O)-, -CH₂-S(O)₂-, -N=C(H)-, -N(H)-C(O)-, -O-C(O)-, -S-C(O)-,
 5 -N=N-, -CH=CH-C(H)-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-C(O)-, -CH₂-
 CH₂-S(O)-, -CH₂-CH₂-S(O)₂-, -CH=CH-C(O)-, -N=CH-C(O)-,
 -O-CH₂-C(O)-, -S-CH₂-C(O)-, and -N(H)-C(O)-C(O)-; or

Y is selected from =C(OH)-; and

E is selected from -CH=CH-C(H)=, -C(O)-C(H)=, -C(O)-N=, -O-N=, -S-N=,
 10 -C(O)-N(H)-N=, -CH=N-N=, -CH=N(O)-N=, and -N(H)-C(O)-N=.

More preferred is a compound of Formula III wherein:

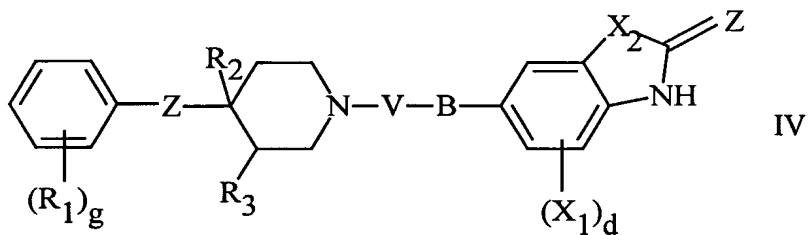
-E-Y- is selected from the group consisting of

-CH=CH-N(H)-,
 -(CH₂)₂-N(H)-,
 15 -CH=N-N(H)-,
 -C(O)-CH₂-N(H)-,
 -CH₂-C(O)-N(H)-,
 -CH₂-S(O)-N(H)-,
 -CH₂-S(O)₂-N(H)-,
 20 -CH=CH-CH(OH)-,
 -(CH₂)₂-CH(OH)-,
 -C(O)-C(H)=C(OH)-,
 -C(O)-N=C(OH)-,
 -N=CH-N(H)-,
 25 -N(H)-C(O)-N(H)-,
 -O-C(O)-NH-,
 -S-C(O)-NH-,
 -O-N=CH(OH)-,
 -S-N=CH(OH)-,
 30 -N=N-N(H)-,

13

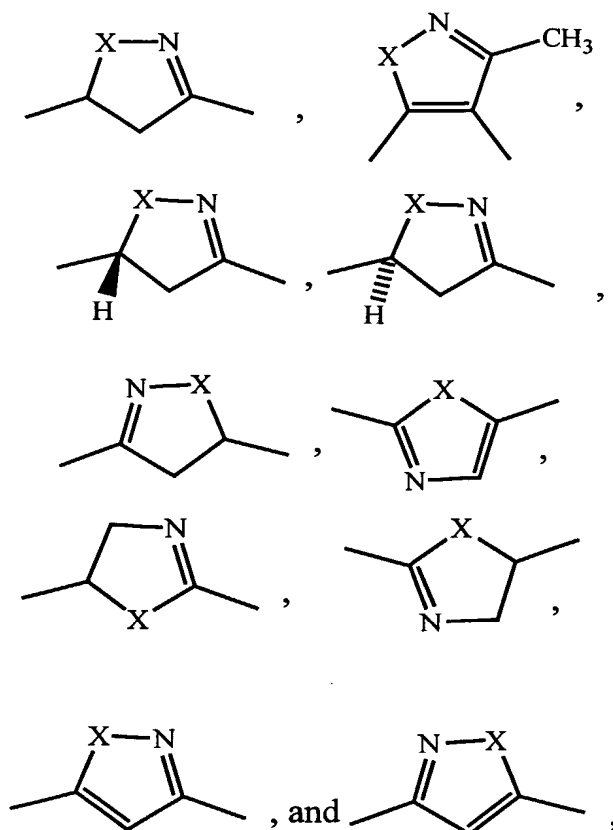
- N=N-N(OH)-,
 -CH=CH-CH=C(OH)-,
 -(CH₂)₃-CH(OH)-,
 -(CH₂)₂-C(O)-N(H)-,
 5 -(CH₂)₂-S(O)-N(H)-,
 -(CH₂)₂-S(O)₂-N(H)-,
 -CH=CH-C(O)-N(H)-,
 -C(O)-NH-N=C(OH)-,
 -CH=N-N=C(OH)-,
 10 -CH=N(O)-N=C(OH)-,
 -N(H)-C(O)-N=C(OH)-,
 -N=CH-C(O)-NH-,
 -O-CH₂-C(O)-NH-,
 -S-CH₂-C(O)-NH-, and
 15 -N(H)-C(O)-C(O)-N(H)-.

Also preferred is a compound of Formula IV



- and pharmaceutically acceptable salts thereof wherein R₁, g, h, R₂, V, B, X₁, and
 d are as defined above for Formula I; and
 20 X₂ is selected from O, S, NH, and CH₂; and
 B is selected from the group consisting of:

14



wherein X is selected from O, S, and N-R, wherein R is hydrogen or alkyl, and wherein Z is selected from O or S.

- 5 More preferred is a compound of Formula IV selected from the group consisting of:

6-[5-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one;

- 6-[5-(4-Benzylpiperidin-1-ylmethyl)-3-methylisoxazol-4-yl]-3*H*-
10 benzoxazol-2-one;

6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one hydrochloride;

(+)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

- (-)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{3-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-5-yl}-3*H*-benzoxazol-2-one;

- 6-{2-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3*H*-benzoxazol-2-one;
- 6-{2-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3*H*-benzothiazol-2-one;
- 5 5-[2-(4-Benzylpiperidin-1-ylmethyl)thiazol-5-yl]-1,3-dihydrobenzimidazole-2-thione;
- 6-{2-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]oxazol-5-yl}-3*H*-benzothiazol-2-one;
- 6-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-3*H*-benzoxazol-2-one;
- 10 5-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-1,3-dihydroindol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydrothiazol-2-yl}-3*H*-benzoxazol-2-one;
- 6-[5-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzoxazol-2-one;
- 15 6-[2-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydrothiazol-5-yl]-3*H*-benzoxazol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]isoxazol-3-yl}-3*H*-benzoxazol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)piperidin-1-yl]methyl}-4,5-dihydroisoxazol-3-yl}-3*H*-benzothiazol-2-one;
- 20 6-[5-(4-Benzyl-4-hydroxypiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)piperidine-1-carbonyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;
- 25 6-(5-{2-[4-(4-Fluorobenzyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)-4-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;
- 30 5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid;

5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid methyl ester;

4-(4-Fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid ethyl ester;

5 4-(4-Fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid;

6-{5-[4-(4-Fluorobenzyl)-3-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{5-[4-(4-Fluorophenoxy)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{5-[4-(4-Fluorophenylsulfanyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{5-[4-(4-Fluorobenzenesulfinyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

15 6-{5-[4-(4-Fluorobenzoyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-(5-{4-[(4-Fluorophenyl)hydroxymethyl]piperidin-1-ylmethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one;

4-Chloro-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-5-methyl-3*H*-benzoxazol-2-one;

-{5-[4-(4-Fluorophenyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

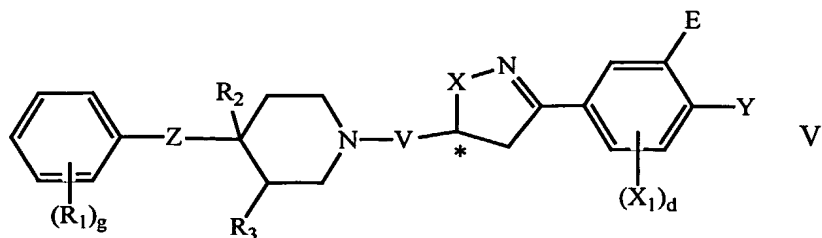
6-[5-(4-Phenyl-4-hydroxy)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one; and

25 6-(5-{2-[4-(4-Fluorophenyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one.

More preferred is a compound of Formula IV named (-)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-3-one.

30 Still more preferred is a compound of Formula IV named (+)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-3-one.

Preferred is a compound of Formula V

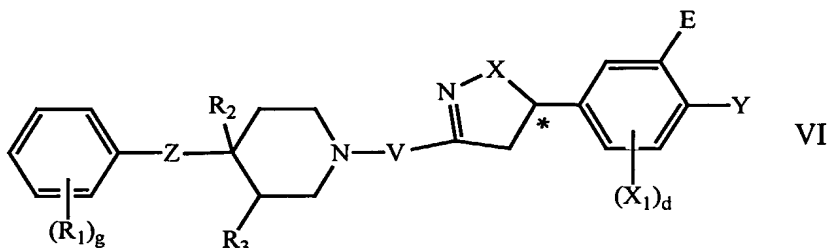


and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 , d , E , and Y are as defined above for Formula I;

5 X is O, S, or N-R, wherein R is hydrogen or alkyl; and

* means a chiral center designated R , S , or mixtures thereof.

Preferred is a compound of Formula VI



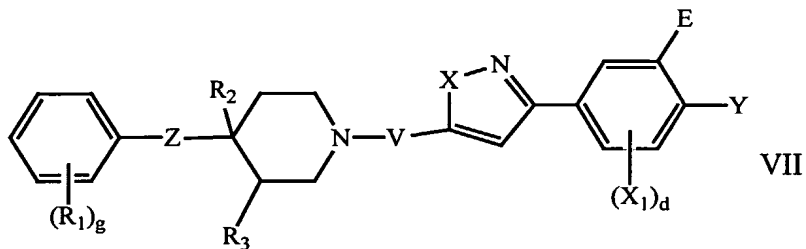
and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

10 d , E , and Y are as defined above for Formula I;

X is O, S, or N-R, wherein R is hydrogen or alkyl; and

* means a chiral center designated R , S , or mixtures thereof.

Preferred is a compound of Formula VII

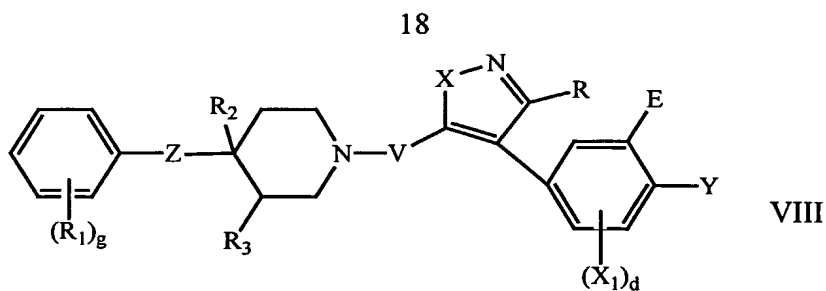


15 and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

d , E , and Y are as defined above for Formula I; and

X is O, S, or N-R, wherein R is hydrogen or alkyl.

Preferred is a compound of Formula VIII

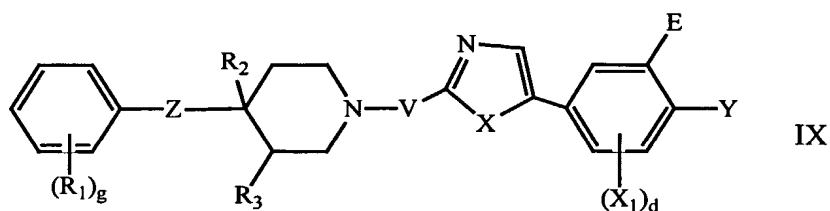


and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

d , E , and Y are as defined above for Formula I; and

X is O, S, or N-R, wherein R is independently hydrogen or alkyl.

5 Preferred is a compound of Formula IX

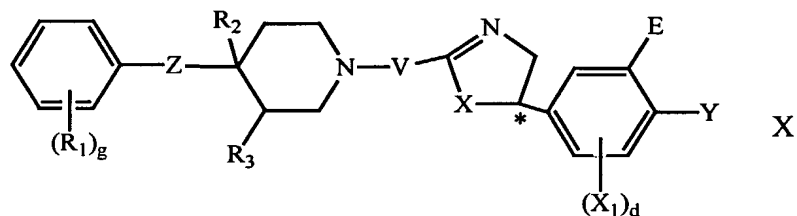


and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

d , E , and Y are as defined above for Formula I; and

X is O, S, or N-R, wherein R is hydrogen or alkyl.

10 Preferred is a compound of Formula X



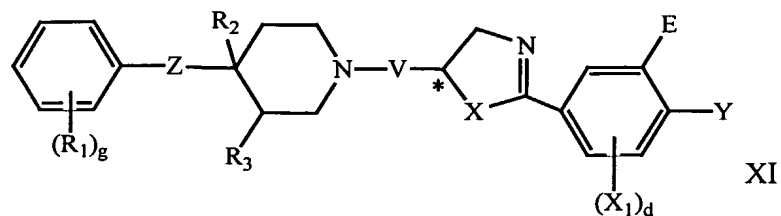
and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

d , E , and Y are as defined above for Formula I;

X is O, S, or N-R, wherein R is hydrogen or alkyl; and

15 * means a chiral center designated R , S , or mixtures thereof.

Preferred is a compound of Formula XI



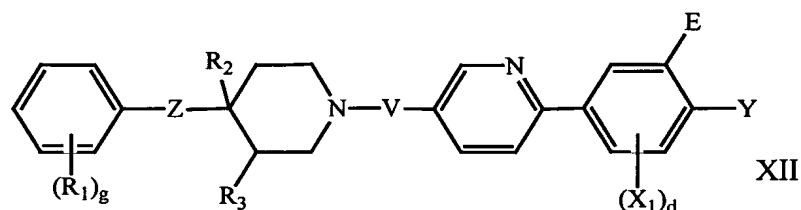
and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

d , E , and Y are as defined above for Formula I;

X is O , S , or $N-R$, wherein R is hydrogen or alkyl; and

* means a chiral center designated R , S , or mixtures thereof.

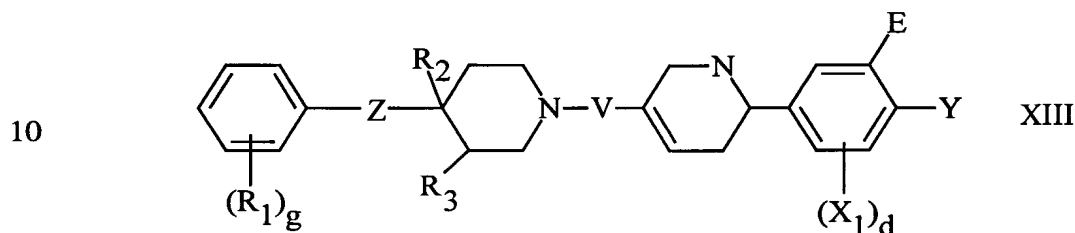
5 Preferred is a compound of Formula XII



and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

d , E , and Y are as defined above for Formula I.

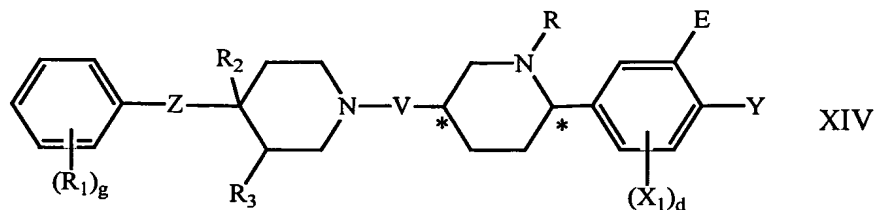
Preferred is a compound of Formula XIII



and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

d , E , and Y are as defined above for Formula I.

Preferred is a compound of Formula XIV



15 and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 ,

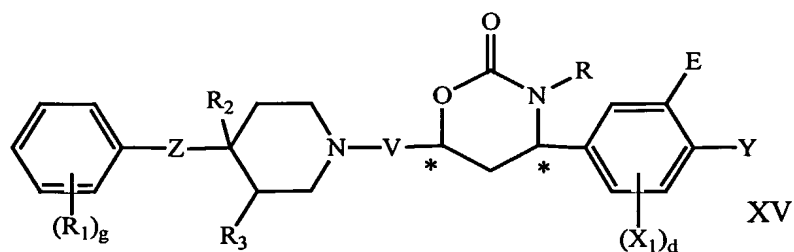
d , E , and Y are as defined above for Formula I;

R is hydrogen or alkyl; and

* means a chiral center designated R , S , or mixtures thereof.

Preferred is a compound of Formula XV

20



and pharmaceutically acceptable salts thereof wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 , d , E , and Y are as defined above for Formula I;

R is hydrogen, alkyl, or substituted alkyl; and

5 * means a chiral center designated R , S , or mixtures thereof.

The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, together with a diluent, carrier, or excipient.

10 In a preferred embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II or Formula IV together with a diluent, carrier, or excipient.

In a more preferred embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound
15 selected from the group consisting of:

(+)-6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-3-one;

(-)-6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-3-one, or

20 a pharmaceutically acceptable salt thereof., together with a diluent, carrier, or excipient.

The invention also provides a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom which comprises administering a
25 compound of Formula I or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the invention provides a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom

comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein the disorders are selected from stroke, cerebral ischemia, central nervous system disorders, depression, trauma, hypoglycemia, neurodegenerative disorders, anxiety, migraine headache, convulsions, aminoglycoside antibiotics-induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal, pain, including chronic pain, neuropathic pain, or surgical pain, and urinary incontinence.

In a more preferred embodiment, the invention provides a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein the disorder is pain.

In another more preferred embodiment, the invention provides a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein the disorder is Parkinson's disease.

In a still more preferred embodiment, the invention provides a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom comprising administering a compound of Formula II or Formula IV.

In a still more preferred embodiment, the invention provides a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom comprising administering a compound selected from the group consisting of:

(+)-6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3H-benzoxazol-3-one;

(-)-6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3H-benzoxazol-3-one, or

a pharmaceutically acceptable salt thereof.

In another more preferred embodiment, the invention provides a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate

receptor subtypes in a mammal, including a human, suffering therefrom comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof, further comprising administering a dopamine agonist.

In another more preferred embodiment, the invention provides a method of
 5 treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof, further comprising administering a dopamine agonist wherein said dopamine agonist is L-DOPA.

10 In another preferred embodiment, the invention provides a method of treating disorders comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof in unit dosage form.

Also, the invention provides a compound selected from the group consisting of:

- 15 6-(2-Azido-1-hydroxyethyl)-3*H*-benzoxazol-2-one;
 6-[2-Azido-1-(*tert*-butyldimethylsilanyloxy)ethyl]-3*H*-benzoxazol-2-one;
 6-[2-Amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-3*H*-benzoxazol-2-one;
 2-(4-Benzylpiperidin-1-yl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]acetamide;
 20 2-(4-Benzylpiperidin-1-yl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]thioacetamide;
 2-(4-Benzylpiperidin-1-yl)-*N*-[2-hydroxy-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]thioacetamide;
 1-Chloro-3-[4-(4-fluorobenzyl)piperidin-1-yl]propan-2-ol;
 25 1-Chloro-3-(4-benzylpiperidin-1-yl)propan-2-ol;
 2-{3-[4-(4-Fluorobenzyl)piperidin-1-yl]-2-hydroxypropyl}isoindole-1,3-dione;
 2-[3-(4-Benzylpiperidin-1-yl)-2-hydroxypropyl]isoindole-1,3-dione;
 1-Amino-3-[4-(4-fluorobenzyl)piperidin-1-yl]propan-2-ol *bis*-
 30 hydrochloride salt;
 1-Amino-3-[4-benzylpiperidin-1-yl]propan-2-ol *bis*-hydrochloride salt;

{3-[4-(4-Fluorobenzyl)piperidin-1-yl]-2-hydroxypropyl}carbamic acid benzyl ester;

[3-(4-Benzylpiperidin-1-yl)-2-hydroxypropyl]carbamic acid benzyl ester;

{2-(*tert*-Butyldimethylsilanyloxy)-3-[4-(4-fluorobenzyl)piperidin-1-yl]propyl}carbamic acid benzyl ester;

{2-(*tert*-Butyldimethylsilanyloxy)-3-[4-benzylpiperidin-1-yl]propyl}carbamic acid benzyl ester;

{2-(*tert*-Butyldimethylsilanyloxy)-3-[4-(4-fluorobenzyl)piperidin-1-yl]propylamine;

10 Methyl 2-oxo-2,3-dihydrobenzoxazole-6-carboxylate;

2-Oxo-2,3-dihydrobenzoxazole-6-carboxylic acid;

2-Oxo-2,3-dihydrobenzoxazole-6-carboxylic acid [3-(4-benzylpiperidin-1-yl)-2-(*tert*-butyldimethylsilanyloxy)propyl]amide;

2-Oxo-2,3-dihydrobenzoxazole-6-carboxylic acid [3-(4-(4-fluorobenzyl)piperidin-1-yl)-2-(*tert*-butyldimethylsilanyloxy)propyl]amide;

2-Oxo-2,3-dihydrobenzoxazole-6-carbothioic acid [3-(4-benzylpiperidin-1-yl)-2-(*tert*-butyldimethylsilanyloxy)propyl]amide;

2-Oxo-2,3-dihydrobenzoxazole-6-carbothioic acid [3-(4-benzylpiperidin-1-yl)-2-hydroxypropyl]amide;

20 6-(2-Azido-1-hydroxyethyl)-3*H*-benzoxazol-2-one;

6-[2-Azido-1-(*tert*-butyldimethylsilanyloxy)ethyl]-3*H*-benzoxazol-2-one;

6-[2-Amino-1-(*tert*-butyldimethylsilanyloxy)ethyl]-3*H*-benzoxazol-2-one;

2-(4-Benzylpiperidin-1-yl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]acetamide;

25 2-(4-Benzylpiperidin-1-yl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]thioacetamide; and

2-(4-Benzylpiperidin-1-yl)-*N*-[2-hydroxy-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]thioacetamide.

Also, the invention provides a process for preparing the compound of
30 Formula I and pharmaceutically acceptable salts thereof comprising the steps of:

1) aminating a precursor alkyl halide;

2) cyclizing the product of Step 1;

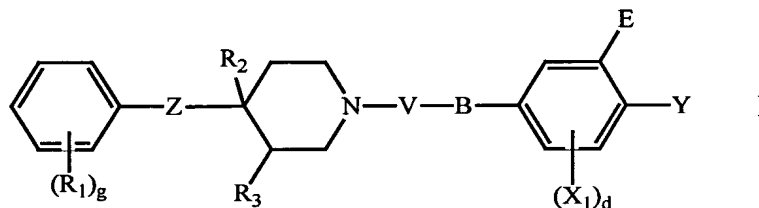
- 3) recovering the desired compound of Formula I; and
- 4) converting, if desired, to a pharmaceutically acceptable salt.

Also, the invention provides a process for preparing the compound of Formula I and pharmaceutically acceptable salts thereof comprising the steps of:

- 5 1) halogenating an unsaturated side chain of a precursor to the compound;
- 2) cyclizing the product of Step. 1;
- 3) recovering the desired compound of Formula I; and
- 4) converting, if desired, to a pharmaceutically acceptable salt.

DETAILED DESCRIPTION OF THE INVENTION

10 As recited above, one aspect of the present invention is a compound of Formula I



and a pharmaceutically acceptable salt thereof, wherein R_1 , g , Z , h , R_2 , R_3 , V , B , X_1 , d , E , and Y are as defined above.

15 All of the references cited herein, including patents, are incorporated herein by reference.

The following definitions apply to terms used in this specification and claims.

The term "patient" means a mammal, including a human.

20 Preferred patients are humans, cats, and dogs.

The term "IC₅₀" means the concentration of test compound required to inhibit activity of a receptor or enzyme by 50%.

The term "L-DOPA" means 3-hydroxy-L-tyrosine.

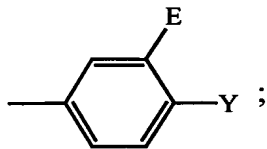
The term " $(X_1)_d$ " wherein d is an integer of from 0 to 2 means the group

25 X_1 is present 0 to 2 times on the phenylene to which it is attached. The groups X_1

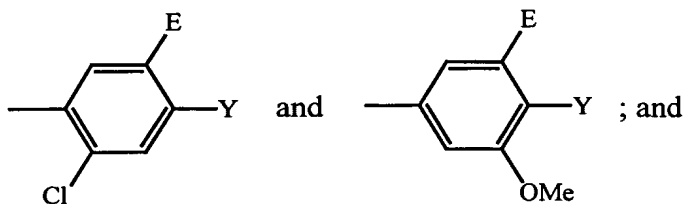
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are independently the same or different. Illustrative examples of substituted phenylenes are drawn below.

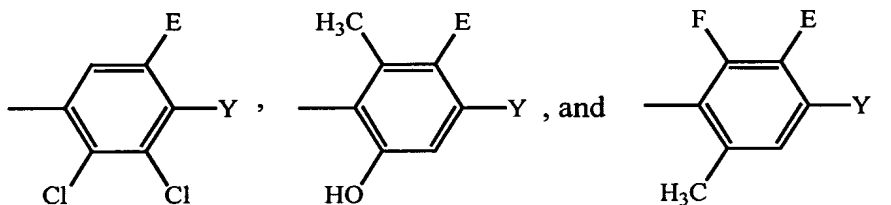
d is 0:



5 d is 1:

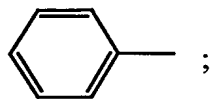


d is 2:

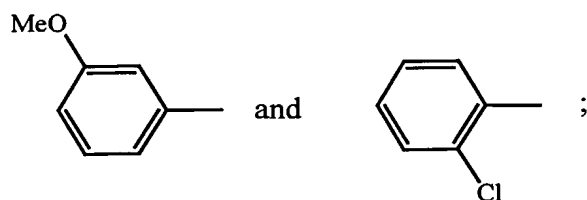


10 Likewise the term “(R₁)_g” wherein g is an integer of from 0 to 3 means the group R₁ is present 0 to 3 times on the phenyl to which it is attached. The groups R₁ are independently the same or different. Illustrative examples of substituted phenyls are drawn below.

g is 0:

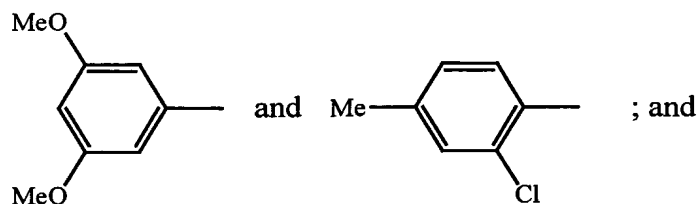


15 g is 1:

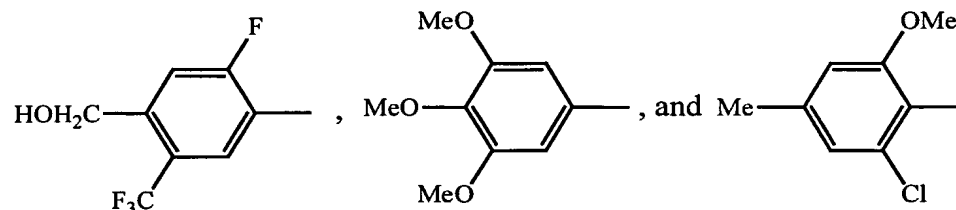


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g is 2:



g is 3:



5 The term “comprising”, which is synonymous with the terms “including”, “containing”, or “characterized by”, is inclusive or open-ended and does not exclude additional, unrecited elements or method steps from the scope of the invention that follows.

10 The phrase “consisting of”, is closed-ended and excludes any element, step, or ingredient not specified in the description of the invention that follows.

The phrase “consisting essentially of” limits the scope of the invention that follows to the specified elements or steps and those further elements or steps that do not materially affect the basic and novel characteristics of the invention.

15 The phrase “filter aid” means a filter medium comprising small particulates. Illustrative examples of filter aids include kieselguhr and CELITE (Celite Corporation, Lompoc, California), a diatomaceous earth filter aid.

The term “alkyl” means a straight or branched, unsubstituted or substituted, hydrocarbon group having from 1 to 12 carbon atoms. Preferred alkyl groups are C₁-C₆ alkyl. Typical examples of unsubstituted alkyl groups include

20 methyl (i.e., CH₃-), ethyl, 1-propyl, and 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 5-methyl-1-hexyl, 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-1-heptyl, 5,5-dimethylhexyl, 1-nonyl, 2-nonyl, 1-decyl, 2-decyl, 1-undecyl, 2-undecyl,

25 1-dodecyl, and 5-dodecyl. Substituted alkyl groups are described below.

The term “alkenyl” means a straight or branched, unsubstituted or substituted, hydrocarbon group having from 2 to 12 carbon atoms and 1 or 2 sites of unsaturation. Preferred groups are C₂-C₆ alkenyl. Illustrative examples of unsubstituted alkenyl groups include ethenyl [i.e., CH₂=C(H)-], 1-propenyl, 2-propenyl, 1-buten-1-yl, 2-buten-1-yl, 1-penten-1-yl, 2-penten-1-yl, 1-penten-3-yl, 1-penten-5-yl, 1-hexen-1-yl, 1-hexen-4-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-octen-3-yl, 5-nonen-2-yl, 4-undecen-4-yl, and 5-dodecen-2-yl. Substituted alkenyl groups are defined below.

The term “alkoxy” means a straight or branched, substituted or unsubstituted, alkyl group of from 1 to 12 carbon atoms linked through an oxygen atom. Preferred is C₁-C₆ alkoxy. Illustrative examples of unsubstituted alkoxy groups include methoxy (i.e., CH₃-O-), ethoxy, isopropoxy, tert-butoxy, iso-pentoxo, octyloxy, and 7,7-dimethyloctyloxy. Substituted alkoxy groups are defined below.

The term “aryl” means an unsubstituted or substituted aromatic carbocyclic ring having 6 or 10 carbon atoms. Illustrative examples of unsubstituted aryl groups include phenyl (i.e., C₆H₅-), 1-naphthyl, and 2-naphthyl. Substituted aryl groups are defined below.

The term “aralkyl” means an unsubstituted or substituted aromatic carbocyclic ring having 6 or 10 carbon atoms (i.e., an aryl group) linked through an alkylene group, wherein alkylene is as defined below. Illustrative examples of unsubstituted aralkyl groups include benzyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 3-methyl-3-phenylpropyl, 1-naphthylmethyl, 1-naphthylethyl, 3-(1-naphthyl)-propyl, 4-(1-naphthyl)-butyl, 4-(2-naphthyl)-butyl, 4-phenylheptyl, and 12-(2-hydroxyphenyl)-dodec-3-yl. Substituted aralkyl groups are defined below.

The term “alkylene” means a straight or branched hydrocarbon chain diradical of from 1 to 12 carbon atoms. Preferred groups are C₁-C₆ alkylene. Illustrative examples of alkylene groups include methylene (i.e., -CH₂-), 1,2-ethylene, 1,2-propylene, 1,3-propylene, 2,2-dimethyl-hexane-1,6-diyl, and dodecan-1,12-diyl.

The term "cycloalkyl" means an unsubstituted or substituted, saturated carbocyclic ring having from 3 to 7 carbon atoms. Illustrative examples of unsubstituted cycloalkyl groups include cyclopentyl, cyclopropyl, cyclohexyl or cycloheptyl. Substituted cycloalkyl is defined below.

5 As discussed above, the groups alkyl, alkenyl, alkoxy, aryl, aralkyl, and cycloalkyl may be substituted. These substituted groups are respectively termed: "substituted alkyl", "substituted alkenyl", "substituted alkoxy", "substituted aryl", "substituted aralkyl", and "substituted cycloalkyl".

The groups can be substituted with from 1 to 3 substituents independently
 10 selected from halogen, OH, O-(C₁-C₆ alkyl), OC(O)-(C₁-C₆ alkyl), -(C₁-C₆ alkylene)-OH, -(C₁-C₆ alkylene)-O-(C₁-C₆ alkyl), NH₂, N(H)-(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)₂, NHC(O)-(C₁-C₆ alkyl), -(C₁-C₆ alkylene)-NH₂, -(C₁-C₆ alkylene)-N(H)-(C₁-C₆ alkyl), -(C₁-C₆ alkylene)-N-(C₁-C₆ alkyl)₂, SH, S-(C₁-C₆ alkyl), S-C(O)-(C₁-C₆ alkyl), -(C₁-C₆ alkylene)-SH, -(C₁-C₆ alkylene)-S-(C₁-C₆ alkyl), unsubstituted cycloalkyl, C(O)-(C₁-C₆ alkyl), CO₂H, CO₂-(C₁-C₆ alkyl), C(O)NH₂, C(O)NH-(C₁-C₆ alkyl), and C(O)N-(C₁-C₆ alkyl)₂, wherein (C₁-C₆ alkyl) means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms, (C₁-C₆ alkylene) means a straight or branched hydrocarbon chain diradical of from 1 to 6 carbon atoms, and unsubstituted
 15 cycloalkyl is as defined above. Further, 1 of the 3 substituents in substituted alkyl, substituted alkenyl (on saturated carbons only), substituted alkoxy, substituted aralkyl (on saturated carbon atoms only) and substituted cycloalkyl may be oxo. Examples of these substituted groups are provided below.

Illustrative examples of substituted alkyl groups include HOCH₂, CF₃,
 25 (CH₂)₄SCH₃, (CH₂)₈NH₂, C(CH₃)₂CH[CO₂C(CH₃)₃]CH₃, CF₂OH, and CH(CO₂H)CH₂CH₂C(O)NMe₂.

Illustrative examples of substituted alkenyl groups include 2-fluoro-ethen-1-yl [i.e., CH(F)=C(H)-], methyl propenoate-2-yl, and 5-iso-butoxy-1-penten-5-yl.

Illustrative examples of substituted alkoxy groups include fluoromethoxy (i.e., $\text{FCH}_2\text{-O-}$), 2-ethoxycarbonyl-ethoxy, 4-aminocarbonyl-oxybutyl, and 8-thiononyloxy [i.e., $\text{CH}_3\text{CH}(\text{SH})\text{-(CH}_2)_7\text{-O-}$].

Illustrative examples of substituted aryl groups include 2-fluorophenyl,
5 2,4,6-trimethoxyphenyl, 4-chloro-2-methylphenyl, 5,6-dichloro-naphth-1-yl, and
8-(dimethylaminomethyl)-naphth-2-yl.

Illustrative examples of substituted aralkyl groups include
4-fluorophenylmethyl, 2-(2,4,6-trimethoxyphenyl)-ethyl, 3-(2-carboxyphenyl)-
propyl, 4-phenyl-4-hydroxy-butyl, 4-(2-dimethylaminomethyl-naphth-1-yl)-butyl,
10 and 12-(2-hydroxyphenyl)-dodec-3-yl.

Illustrative examples of substituted cycloalkyl groups include 3-methylcyclopentyl, 4-hydroxy-cyclohexyl, and 1-methoxy-cycloheptyl.

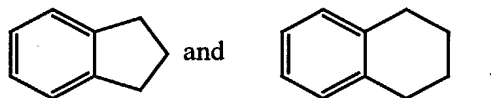
The term “heteroatom” includes nitrogen, oxygen, and sulfur. When the heteroatom is incorporated in a nonaromatic ring, the heteroatom further includes



The term “oxo” means $=\text{O}$.

The term “oxo-substituted” means any group which contains a carbon atom that is substituted with an oxo group (i.e., $=\text{O}$). A carbon atom substituted with an oxo group forms a carbonyl group of formula $\text{C}=\text{O}$.

20 The phrase “fused 9- or 10-membered bicyclic ring containing from 0 to 3 heteroatoms” means a group wherein 2 ring systems share 2 and only 2 atoms. Illustrative examples of a fused bicyclic group containing 0 heteroatoms include



The term “halogen” means bromine, chlorine, fluorine, or iodine.

25 The term “aminoalkyl” means a H_2N group linked through an alkylene group, wherein alkylene has the meaning as defined above. Illustrative examples of aminoalkyl groups include aminomethyl (i.e., $\text{H}_2\text{N-CH}_2\text{-}$), 3-aminopropyl, and 1-amino-1,1-dimethylethyl.

The term "alkylaminoalkyl" means an alkyl group, linked through an N(H) group, which in turn is linked through an alkylene group, wherein alkyl and alkylene are as defined above. Illustrative examples of alkylaminoalkyl groups include methylaminomethyl (i.e., $\text{CH}_3\text{NHCH}_2-$), 3-(tert-butylamino)-propyl, and
5 6-(hexylamino)-hexyl.

The term "hydroxyalkyl" means an OH group linked through an alkylene group, wherein alkylene has the meaning defined above. Illustrative examples of hydroxyalkyl groups include hydroxymethyl, 2-hydroxyethyl, and 2-hydroxy-1,1-dimethylethyl.

10 The term "(aminocarbonyl)-alkyl" means an $\text{C}(\text{O})\text{NH}_2$ group linked through an alkylene group, wherein alkylene has the meaning defined above. Illustrative examples of (aminocarbonyl)-alkyl groups include $\text{H}_2\text{NC}(\text{O})-\text{CH}_2-$ and $\text{H}_2\text{NC}(\text{O})-\text{C}(\text{CH}_3)_3$.

The term "(alkylthio)-alkyl-" means an alkyl group linked through a sulfur
15 atom, which in turn is linked through an alkylene group, wherein alkyl and alkylene have the meanings defined above. Illustrative examples of (alkylthio)-alkyl groups include $\text{CH}_3-\text{S}-\text{CH}_2-$, $\text{CH}_3\text{CH}_2-\text{S}-(\text{CH}_2)_2-$, and $\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{C}(\text{CH}_3)_2-\text{S}-\text{C}(\text{CH}_3)_2\text{CH}_2-$.

The term "carboxyalkyl" means a CO_2H group linked through an alkylene
20 group, wherein alkylene has the meaning defined above. Illustrative examples of carboxyalkyl groups include carboxymethyl, 2-carboxyethyl, and 2-carboxy-1,1-dimethylethyl.

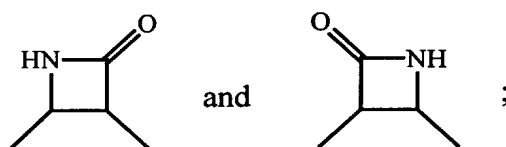
The term "amino" means the $-\text{NH}_2$ group.

The term "haloalkyl" means a halogen linked through an alkylene group,
25 wherein halogen and alkylene are as defined above. Illustrative examples of haloalkyl include trifluoromethyl, difluoromethyl, fluoromethyl, and 2,2,2-trichloroethyl.

The term " $\text{C}(\text{O})$ -alkyl" means an alkyl group as defined above linked through a carbonyl carbon atom. Illustrative examples of $\text{C}(\text{O})$ -alkyl groups
30 include acetyl (i.e., $\text{C}(\text{O})\text{CH}_3$), 2,2-dimethylpropionyl, and dodecanoyl.

The term "heterocyclene" means a 4-, 5-, or 6-membered, carbon-linked, unsubstituted or substituted with, for example, alkyl, carboxylic acid, or ester, heterocyclic diradical ring, containing from 1 to 3 heteroatoms which are N, O, or S, selected from the group consisting of:

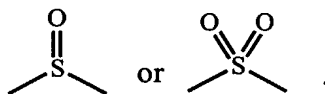
- 5 (i) 1-aza-2-cyclobutanon-3,4-diyl of formula



- (ii) a 5-membered aromatic, nonaromatic dihydro, or nonaromatic tetrahydro ring having carbon atoms and from 1 to 3 heteroatoms selected from N, O, and S;
- 10 (iii) a 5-membered oxo-substituted nonaromatic tetrahydro ring having carbon atoms and 1 or 2 heteroatoms selected from N, O, and S;
- (iv) a 6-membered aromatic, nonaromatic tetrahydro, or nonaromatic hexahydro ring having carbon atoms and 1 or 2 heteroatoms, which heteroatoms are nitrogen, and
- 15 (v) a 6-membered nonaromatic oxo-substituted hexahydro ring having carbon atoms and 1 or 2 heteroatoms which are nitrogen and 0 or 1 heteroatom which is oxygen;

wherein the radical atoms of the heterocyclene are carbon atoms, and further wherein when B is a nonaromatic heterocyclene containing sulfur, said sulfur may

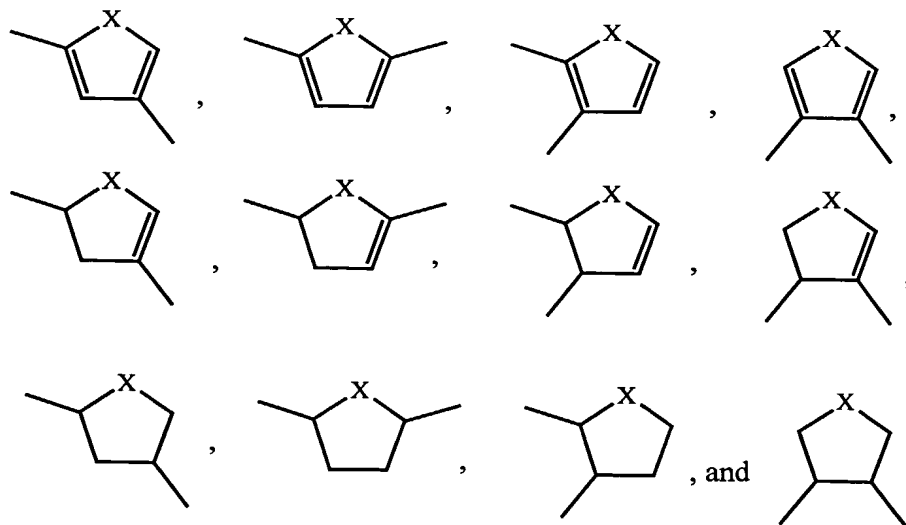
- 20 further comprise



Illustrative examples of 5- and 6-membered heterocyclenes include:

- 1) A 5-membered heterocyclic ring having one heteroatom such as, for example, the following rings:

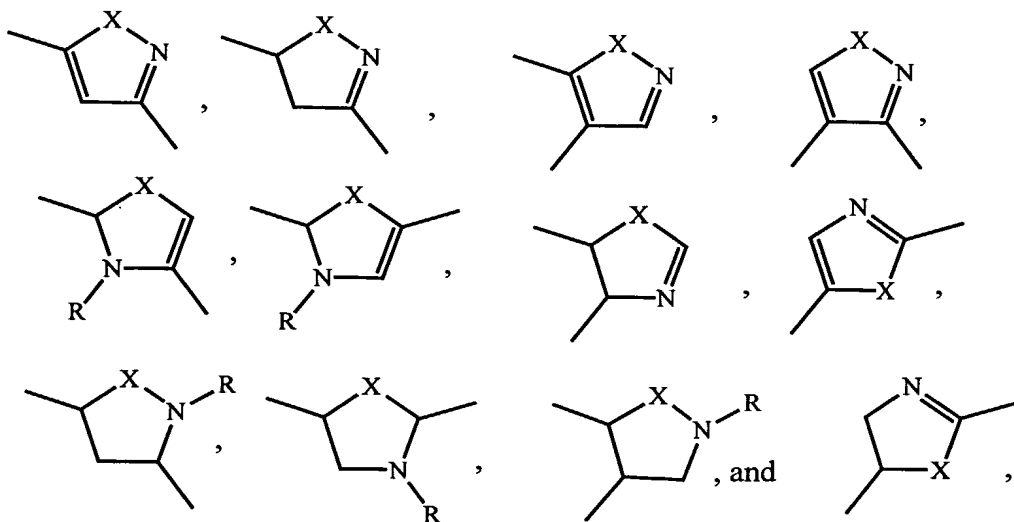
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wherein X is O, S, or N-R wherein R is H or alkyl.

- 2) A 5-membered, substituted or unsubstituted, wherein "substituted" is defined as above, heterocyclic ring having 2 heteroatoms such as, for example, the following rings:

5

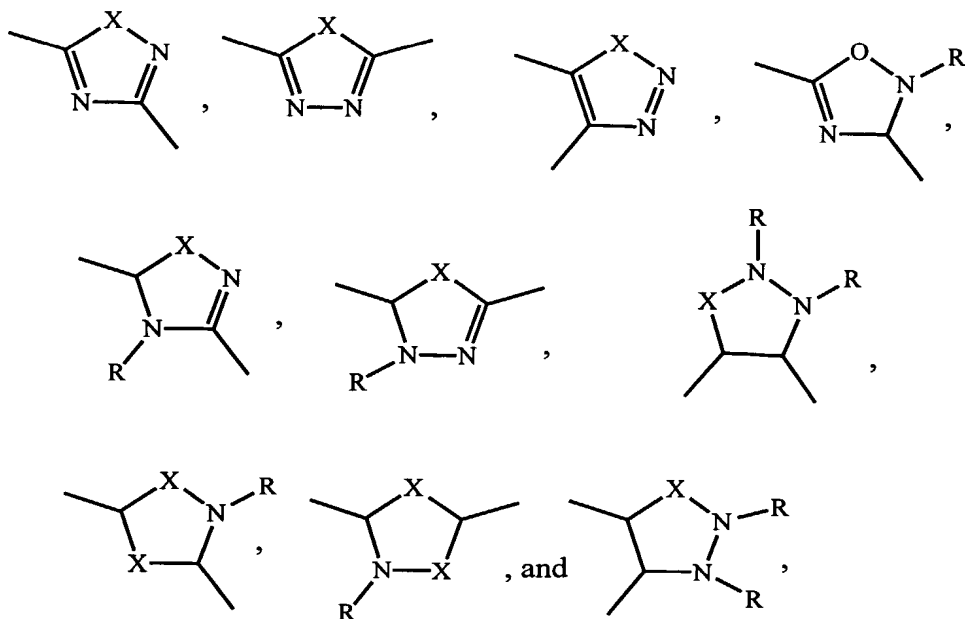


wherein X and R are as defined above.

- 3) A 5-membered heterocyclic ring having 3 heteroatoms such as, for example, the following rings:

10

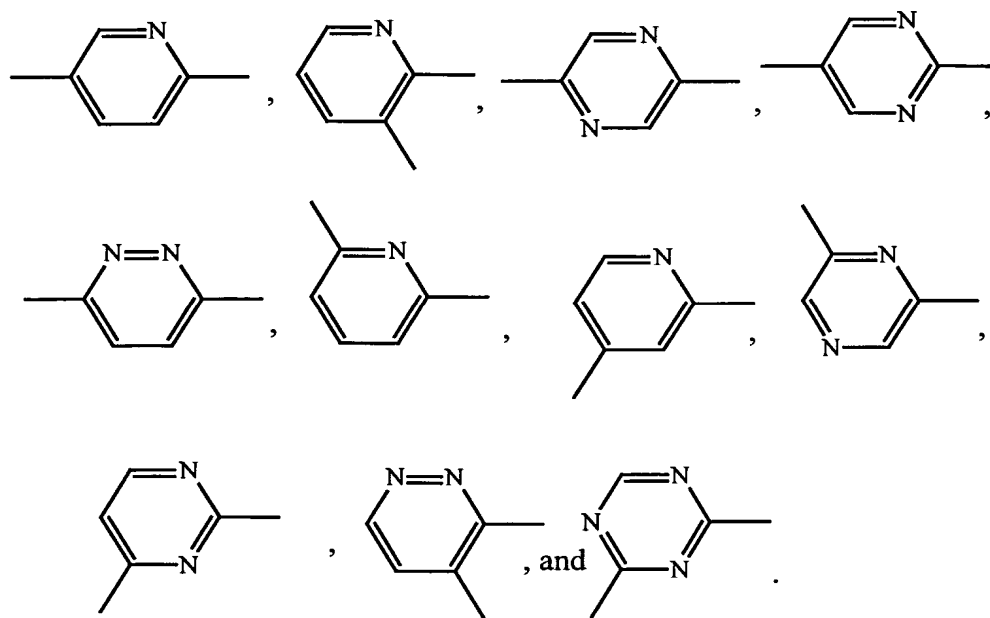
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wherein X and R are as defined above.

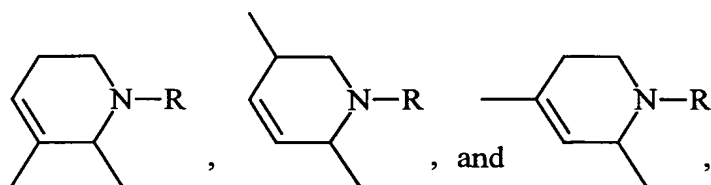
- 4) A 6-membered aromatic heterocyclic ring having 1 to 3 nitrogen atoms such as, for example, following rings:

5



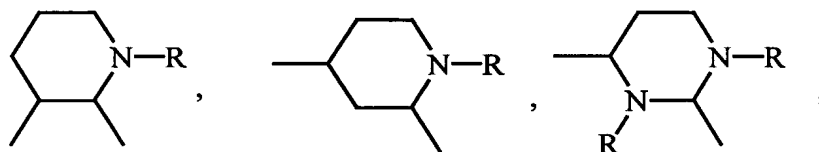
- 5) A 6-membered nonaromatic tetrahydro heterocyclic ring having 1 or 2 nitrogen atoms such as, for example, the following rings:

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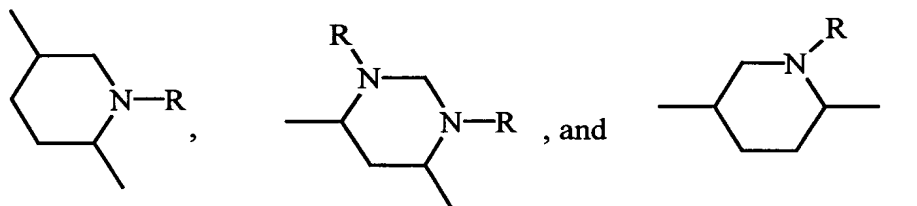


wherein R is independently hydrogen or alkyl;

- 6) A 6-membered nonaromatic hexahydro heterocyclic ring having 1 or 2 nitrogen atoms such as, for example, the following rings:

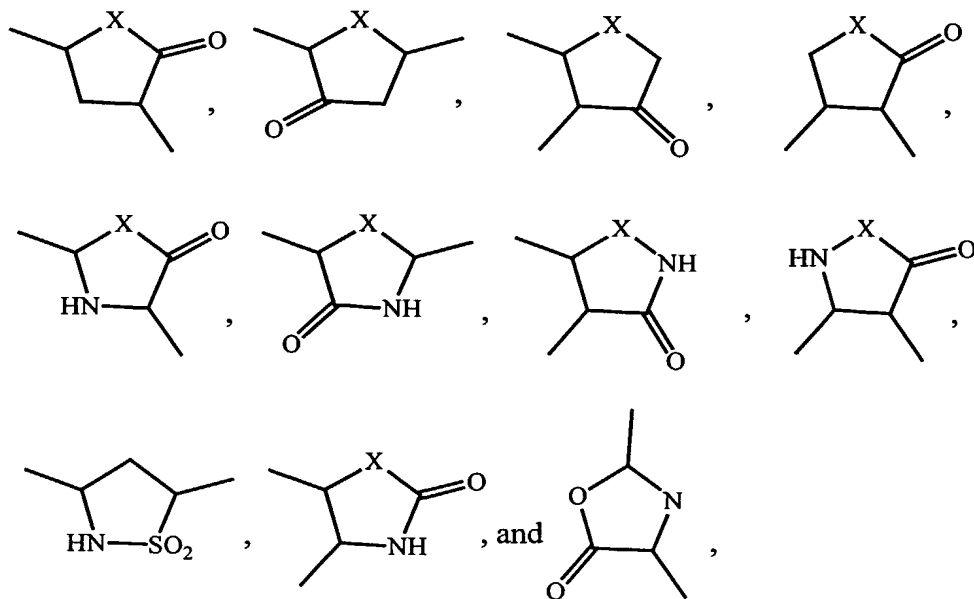


5



wherein R is independently hydrogen or alkyl;

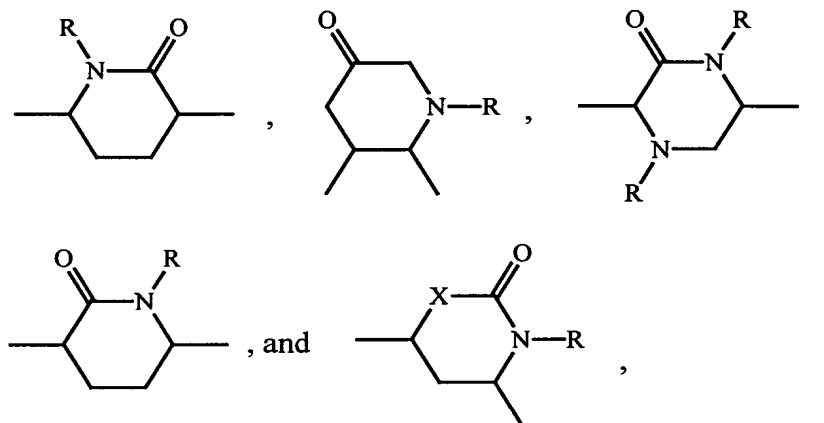
- 7) A 5-membered oxo-substituted heterocyclic nonaromatic tetrahydro ring having 1 or 2 heteroatoms O, S, or N-R such as, for example, the following rings:



10

wherein X and R are as defined above.

- 8) A 6-membered oxo-substituted hexahydro nonaromatic heterocyclic rings having 1 or 2 nitrogen atoms, and 0 or 1 heteroatoms selected from O and S, such as, for example, the following rings:



It is to be appreciated that the above rings do not represent all possible isomers or rings that are described above by the term "heterocyclene".

- 10 It is also to be appreciated that the compounds of Formula I may have chiral centers, in which case all stereoisomers thereof, both separately and as racemic and/or diastereoisomeric mixtures, are included.

Some of the compounds of Formula I are capable of further forming nontoxic pharmaceutically acceptable acid-addition and/or base salts. All of these forms are within the scope of the present invention.

- 15 For example, pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinates suberate, sebacate, fumarate,
- 20

maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, malate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 1977;66:1-19).

The acid addition salts of basic invention compounds are prepared by contacting the free base form of the invention compounds with a sufficient amount of the desired acid to produce the salt in the conventional manner.

Pharmaceutically acceptable base salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, *N*-methylglucamine, and procaine (see, for example, Berge, supra., 1977).

Base salts of acidic invention compounds are prepared by contacting the free acid form of the invention compounds with a sufficient amount of the desired base to produce a salt in the conventional manner.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

The compounds of the invention may be prepared by a number of methods well known to a person of average skill in the arts of organic and medicinal chemistries.

It should be appreciated that the organic and medicinal chemistry arts provide the skilled artisan with electronically searchable literature, reaction, and reagent databases and a wide variety of commercially available starting materials. For example, see the databases of the Chemical Abstracts service (Columbus, Ohio); Katritzky, Alan R., *Handbook of Heterocyclic Chemistry*, Pergamon Press, Ltd., 1985, Volumes 4 and 5; and The Aldrich Catalog (Sigma-Aldrich Corporation, St. Louis, Missouri).

For examples of the preparation of optically pure Δ^2 -isoxazolines (i.e., chiral Δ^2 -isoxazolines that consist of only one enantiomer, or substantially one enantiomer), see Yang, K-S, et al., *Tetrahedron Letters*, 2000;41:1453-1456 or Shimizu, M. et al., *Chemistry Letters*, 1996:455-456.

5 As described above, some of the invention compounds possess chiral centers. It should be appreciated that a person skilled in the medicinal and organic chemistry arts is able to prepare chiral invention compounds by classical resolution techniques and/or asymmetric synthesis.

It should also be appreciated for purposes of synthesizing the compounds
10 of the invention that reactive functional groups present in starting materials, reaction intermediates, or reaction products may be protected during chemical reactions using protecting groups which render the reactive functional groups substantially inert to the reaction conditions (see for example, *Protective Groups in Organic Synthesis*, 2nd ed., Green TW and Wuts PG, John Wiley & Sons, New
15 York, NY 1991). Thus, for example, protecting groups such as the following may be utilized to protect suitable amino, hydroxyl, and other groups of related reactivity: carboxylic acyl groups, such as formyl, acetyl, trifluoroacetyl; alkoxycarbonyl groups, such as ethoxycarbonyl, *t*-butoxycarbonyl (BOC), β,β,β -trichloroethoxycarbonyl (TCEC), β -iodoethoxycarbonyl; aryloxycarbonyl
20 groups, such as benzyloxycarbonyl (CBZ), *p*-methoxybenzyloxycarbonyl, phenoxycarbonyl; trialkyl silyl groups, such as trimethylsilyl and *t*-butyldimethylsilyl (TBDMS); and groups such as trityl, tetrahydropyranyl, vinyloxycarbonyl, *o*-nitrophenylsulfenyl, diphenylphosphinyl, *p*-toluenesulfonyl, and benzyl may all be utilized. The protecting group may be removed, after
25 completion of the synthetic reaction of interest, by procedures known to those skilled in the art. For example, a BOC group may be removed by acidolysis, a trityl group by hydrogenolysis, TBDMS by treatment with fluoride ions, and TCEC by treatment with zinc. Use of protecting groups in organic synthesis is well within the skill of the average artisan.

30 It should be appreciated that reagents, solvents, and starting materials necessary for the preparation of the compounds of the invention may be purchased

from a number of commercial sources or may be readily prepared by a number of methods well known to one of average skill in the art of organic chemistry.

Further, reactions used to prepare the invention compounds can be carried out under a wide variety of conditions comprising solvents, reagents, catalysts,

5 temperatures, time, atmosphere, and pressure.

Many different methods may be used to prepare the invention compounds.

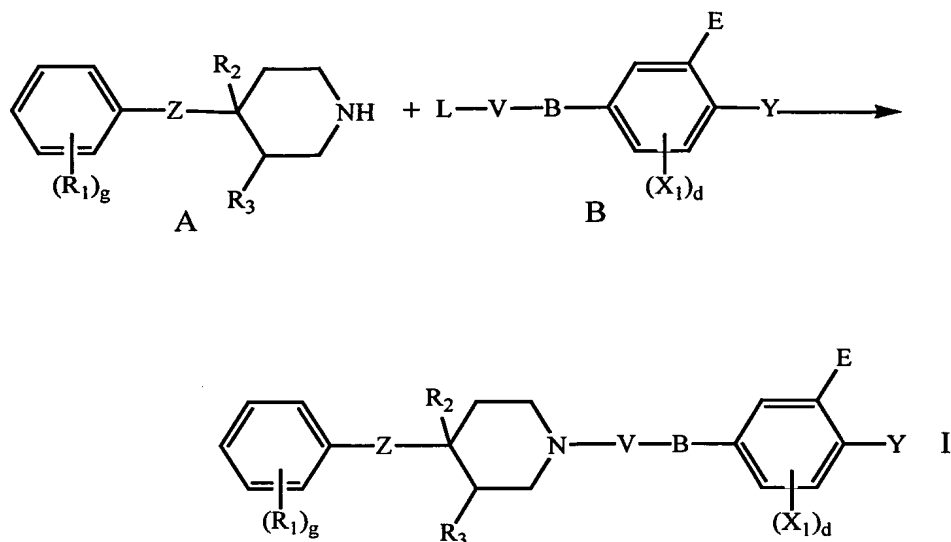
However for purposes of practicing the invention, which comprises compounds, pharmaceutical compositions, and methods of treating certain disorders and diseases, it does not matter how the compounds are made. Nevertheless, novel

10 methods of preparing the invention compounds are valuable as they may afford improvements in ease of synthesis or purification, cost of preparation, or process time. As discussed above, the invention provides novel methods of making the invention compounds.

For example, one method of preparing the compounds of the invention is
15 described below in Scheme 1.

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Scheme 1



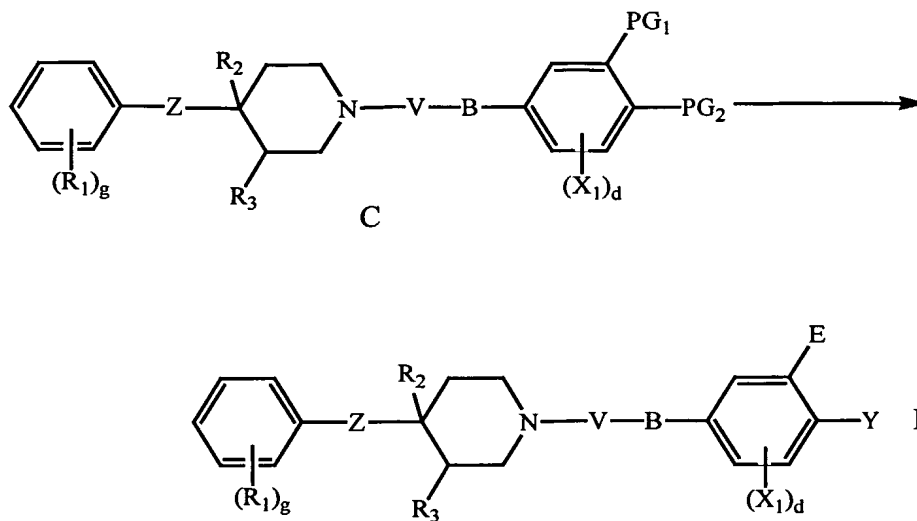
wherein R_1 , g , Z , h , R_2 , R_3 , V , B , X_1 , d , E , and Y are as defined above and L is a leaving group such that when V is $(CH_2)_n$ or $(CH_2)_m-C=O$, wherein m is not 0, L is, for example, halogen, $CH_3CO_2^-$, $CF_3CO_2^-$, $CF_3SO_3^-$, p -toluyl- SO_3^- , and the like; and when V is $C=O$, L is, for example, halogen, hydroxy, which can form intermediates activated for displacement by a compound of formula A by reaction with coupling agents such as, for example, carbonyldiimidazole (CDI), N,N' -dicyclohexylcarbodiimide (DCC), and the like, benzotriazol-1-yl, imidazol-1-yl, $CH_3CO_2^-$, and the like.

In Scheme 1, a compound of formula A, wherein R_1 , g , and R_2 are as defined above, is allowed to react with a compound of formula B, wherein L is a leaving group which is displaced by a compound of formula A, to provide a compound of Formula I. In a preferred procedure, a compound of formula A is dissolved or suspended in an aprotic, polar solvent such as, for example, N,N -dimethylformamide (DMF), ethyl acetate, dimethylsulfoxide (DMSO), acetonitrile, nitromethane, acetone, and the like, and optionally a 1 to 2 molar equivalents of a non-nucleophilic base such as, for example, triethylamine, diisopropylethylamine, sodium hydride, and the like is added, followed by addition of a compound of formula B as a neat material (i.e., only the material itself in solid or liquid form) or in a solution of an aprotic, polar solvent such as, for example, the aprotic, polar solvents recited above, at an addition rate that

maintains a desired reaction temperature, and the mixture is stirred in air or under an inert atmosphere such as, for example, nitrogen or argon, to give a compound of Formula I. In another preferred procedure, a compound of formula A is dissolved or suspended in an aprotic, nonpolar solvent such as, for example, tetrahydrofuran (THF), diethylether, hexanes, and the like, and about one molar equivalent of a strong base such as, for example, n-butyl lithium, sec-butyl lithium, tert-butyl lithium, potassium hexamethyldisilazide (KHMDs), and the like is added, followed by addition of a compound of formula B as a neat material or in a solution of a nonpolar, aprotic solvent such as, for example, the nonpolar, aprotic solvents recited above, at an addition rate that maintains a desired reaction temperature, and the mixture is stirred to give a compound of Formula I. In still another preferred procedure, a compound of formula B, wherein L-V- is HO-C(O)-, is dissolved or suspended in an aprotic solvent such as, for example, THF, DMF, ethyl acetate, and the like, and about 1 molar equivalent of a coupling agent such as, for example, CDI, DCC, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), and the like, followed by addition of a compound of formula A as a neat material or in a solution of an aprotic solvent such as, for example, the aprotic solvents recited above, at an addition rate that maintains a desired reaction temperature, and the mixture is stirred to give a compound of Formula I. In Scheme 1, the preferred molar ratio of a compound of formula A to a compound of formula B is about 1:1.

Another method of preparing the compounds of the invention is described below in Scheme 2.

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Scheme 2



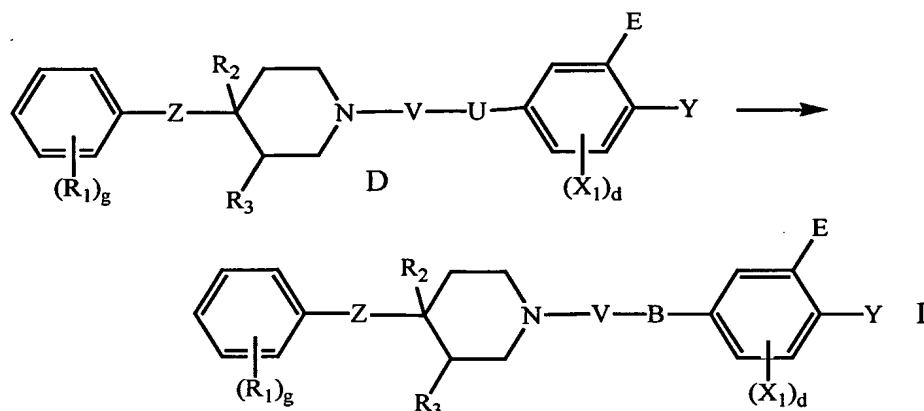
wherein R_1 , g , Z , h , R_2 , R_3 , V , B , X_1 , d , E , and Y are as defined above, and PG_1 and PG_2 are protecting groups which may be deprotected to provide the groups E and Y , respectively, of compounds of Formula I. Illustrative examples of PG_1 are hydrogen (when E is H), -O-benzyl, -S-benzyl, -NH-benzyl, -NH-(4-methoxybenzyl), -NH-BOC, -NH-CBZ, -O-TBDMS, -CH₂-halo, C(O)-CH₂-halo, -CO₂Me, C(O-CH₂)₂, CH₂CH₂CO₂Me, and the like. Illustrative examples of PG_2 are -NH-benzyl, -NH-(4-methoxybenzyl), -NH-BOC, -NH-CBZ, CO₂Me, -O-benzyl, -O-TBDMS, and the like.

In Scheme 2, a compound of formula C is deprotected to give a compound of Formula I. In a preferred procedure, a compound of formula C, wherein PG_1 and/or PG_2 is -O-benzyl, -S-benzyl, -NH-benzyl, -NH-CBZ, and the like, is dissolved or suspended in a suitable solvent such as, for example, acetic acid, ethanol, THF, dichloromethane, and the like, and allowed to react with a deprotecting reagent such as, for example, a mixture of hydrogen gas and a suitable hydrogenation catalyst such as, for example, palladium on carbon, palladium on barium sulfate, platinum on carbon, sponge nickel, and the like, under pressure, phosphorous tribromide, hydrochloric acid, titanium tetrachloride, and the like, at an addition rate that maintains a desired reaction temperature, to give a compound of Formula I. Examples 1, 3, 4a, 4b, 5, and 9 are representative of the chemistry described in Scheme 2.

Another method of preparing the compounds of the invention is described below in Scheme 3.

43

Scheme 3



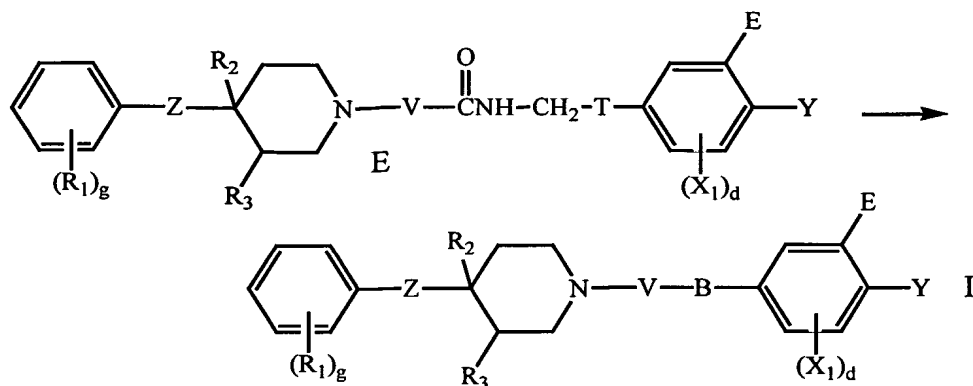
wherein R_1 , g , Z , h , R_2 , R_3 , V , B , X_1 , d , E , and Y are as defined above, and U is -
 $C(H)=C(H)-$ or $-C\equiv C-$.

- 5 In Scheme 3, a compound of formula D is allowed to react with a 3- or 4-membered cyclization reagent to give a compound of Formula I, wherein B is a 5- or 6-membered heterocyclene, respectively. In a preferred procedure, a compound of formula D is dissolved or suspended in an aprotic solvent such as, for example, THF, dichloromethane, acetone, DMF, and the like, and allowed to
- 10 react with a 3-membered cyclizing reagent such as, for example, an alkylazide, alkyl diazomethane, acetonitrile oxide, prepared by reaction of an aldoxime such as, for example, acetaldoxime [i.e., $CH_3C(H)=N-OH$] with a radical generating agent such as, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), and the like, or a 4-membered cyclizing reagent such as, for example, $H_2C=C(H)-$
- 15 $C(H)=N-EDG$, wherein EDG is an electron donating group such as, for example, $-N(CH_3)_2$, $-OMe$, and the like, to give a compound of Formula I. Example 2 is representative of the chemistry described in Scheme 3.

Another method of preparing the compounds of the invention is described below in Scheme 4.

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Scheme 4

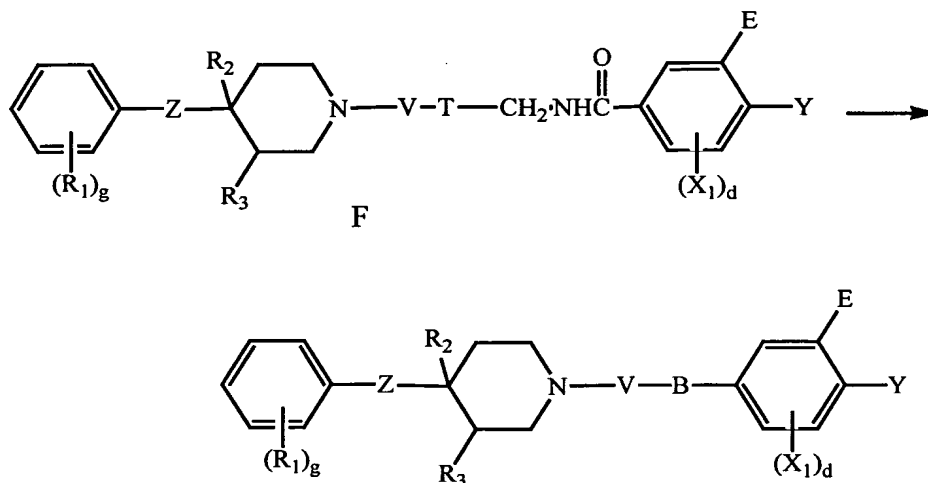


wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 , d , E , and Y are as defined above, B is oxazole, dihydrooxazole, thiazole, or dihydrothiazole, and T is $C=O$ or $C(H)OH$.

- 5 In Scheme 4, a compound of formula E is allowed to react with a reagent and/or catalyst under cyclizing conditions to provide a compound of Formula I. In a preferred procedure, a compound of formula D is dissolved in an aprotic solvent such as, for example, THF, ethyl acetate, DMF, DMSO, and the like, and a dehydrating reagent such as, for example, anhydrous magnesium sulfate,
- 10 anhydrous calcium chloride, activated 3 angstrom molecular sieves, trimethoxymethane, oxalyl chloride, PCl_5 , phosphorous pentoxide and the like, is added and optionally an acid catalyst such as, for example, trifluoroacetic acid, para-toluenesulfonic acid, and the like, is added, and the mixture is stirred to provide a compound of Formula I, wherein B is oxazole or dihydrooxazole. In
- 15 another preferred procedure, a compound of formula D is dissolved in an aprotic solvent such as, for example, THF, ethyl acetate, DMF, DMSO, and the like, and a sulfurating reagent (i.e., a reagent that introduces a sulfur atom) such as, for example, P_2S_5 , [2,4-bis(4-methoxyphenyl)-1,3-dithian-2,4-diphosphetane-2,4-disulfide] (i.e., Lawesson's reagent), and the like, is added, and the mixture is
- 20 stirred to provide a compound of Formula I, wherein B is thiazole or dihydrothiazole. Examples 6(a)-6(f) and 8 are representative of the chemistry described in Scheme 4.

Another method of preparing the compounds of the invention is described below in Scheme 5.

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Scheme 5



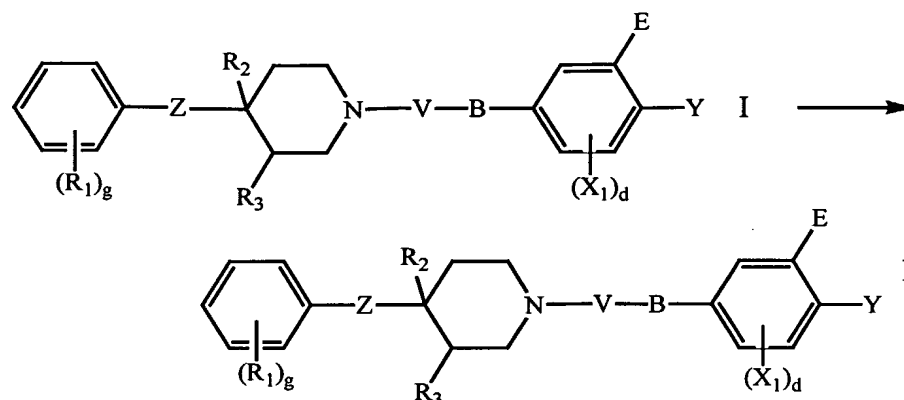
wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 , d , E , and Y are as defined above, B is oxazole, dihydrooxazole, thiazole, or dihydrothiazole, and T is $C=O$ or $C(H)OH$.

- 5 In Scheme 5, a compound of Formula F is allowed to react with a reagent and/or catalyst under cyclizing conditions to provide a compound of Formula I. Preferred procedures are as described above in Scheme 4. Examples 7(a) and 7(b) are representative of the chemistry described in Scheme 5.

- 10 Another method of preparing the compounds of the invention is described below in Scheme 6.

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Scheme 6



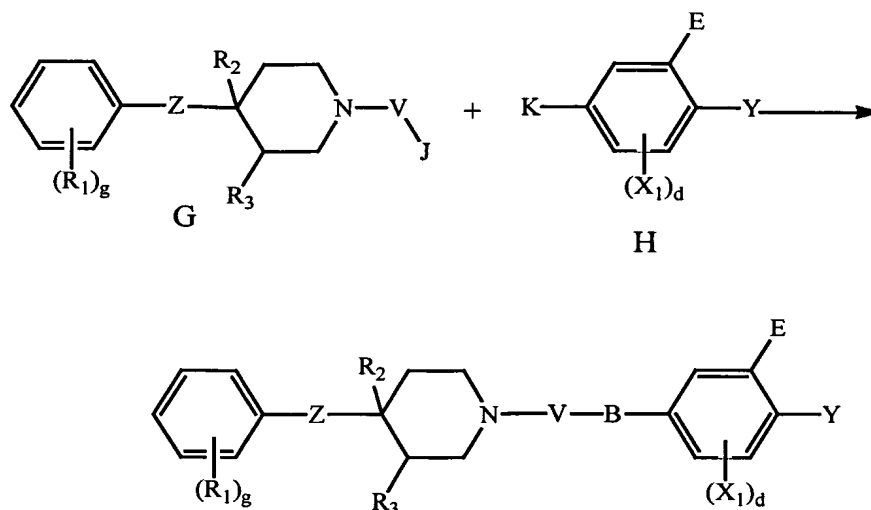
wherein R_1 , g , Z , h , R_2 , R_3 , V , B , X_1 , d , E , and Y are as defined above.

- In Scheme 6, a compound of Formula I is allowed to react with a reagent to
- 5 provide a different compound of Formula I. In a preferred procedure, a compound of Formula I wherein V is $(CH_2)_mC=O$ is dissolved or suspended in a suitable aprotic, nonpolar solvent such as, for example, THF, methyl-*tert*-butylether (MTBE), hexanes, and the like, and a reducing agent such as, for example, lithium aluminum hydride, sodium borohydride, sodium triacetoxyborohydride,
- 10 diisobutylaluminum hydride (DIBAL), and the like, is added at an addition rate that maintains a desired reaction temperature, and the mixture is stirred to give a compound of Formula I wherein V is $(CH_2)_n$.

Another method of preparing the compounds of the invention is described below in Scheme 7.

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Scheme 7



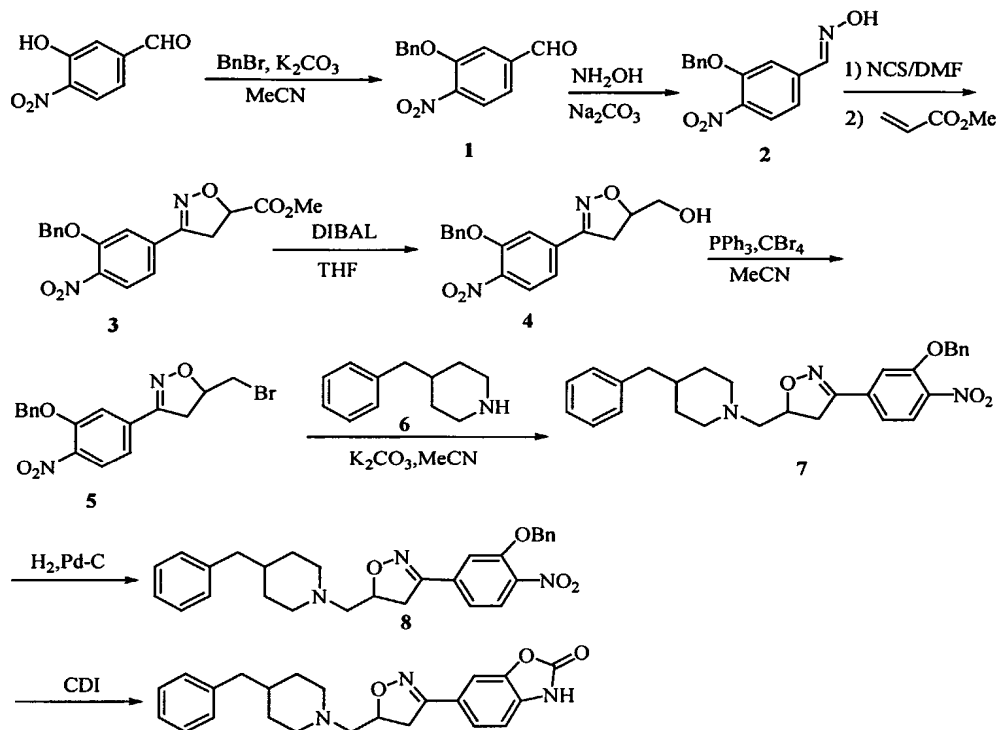
wherein R_1 , g , Z , h , R_2 , R_3 , V , X_1 , d , E , and Y are as defined above, B is isoxazole, dihydroisoxazole (i.e., isoxazoline), dihydrothiazoline, or oxazole; J is $C(H)=CH_2$ or $C\equiv C-H$, and K is $C(Cl)=N-OH$.

In Scheme 7, a compound of formula G is allowed to react with a compound of formula H under [3+2] cyclization conditions to provide a compound of formula I . In a preferred procedure, a compound of formula G and a compound of formula H are dissolved or suspended in a solvent such as, for example, methanol, ethanol, THF, ethyl acetate, toluene, dichloromethane, and the like, and optionally a non-nucleophilic base such as, for example, triethylamine, diisopropylethylamine, sodium hydride, and the like is added, and the mixture is stirred to provide a compound of Formula I . Examples 10 to 16 are representative of the chemistry described in Scheme 7.

Examples of the preparation of the invention compounds are described below.

EXAMPLE 1

6-[5-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one



- 5 **Step 1:** A mixture of 3-hydroxy-4-nitrobenzaldehyde (10.0 g, 0.0598 mol), benzyl bromide (7.20 mL, 0.0598 mol) and anhydrous potassium carbonate (18.20 g, 0.1316 mol) in 250 mL MeCN was heated at 60°C for 5 hours with vigorous stirring. The reaction mixture was filtered, and the filtrate was concentrated. The residue was taken up in chloroform, and an orange precipitate was removed. The filtrate was re-concentrated to an oil which crystallized on standing to give **1** (15.38 g, 100%): TLC R_f = 0.58 (1:1 hexanes/EtOAc).

- 10 **Step 2:** To a suspension of compound of formula **1** (3.0 g, 0.0117 mol) in 30 mL isopropanol was added hydroxylamine hydrochloride (812 mg, 0.0117 mol), followed by sodium carbonate (2.47 g, 0.0234 mol). After addition was complete the reaction mixture was vigorously stirred at 40°C for 30 minutes (all starting material went into solution) and concentrated. The residue was taken up in water, and the aqueous mixture was washed 2X with EtOAc. The organic washings were combined and washed with saturated NaCl(aq), dried over magnesium sulfate and

concentrated to a yellow solid which was used without further purification to give **2** (2.63 g, 82%); TLC R_f = 0.55 (1:1 hexanes/EtOAc); CI-MS (m/z): 273 $[M + H]^+$.

Step 3: Compound of formula **2** (2.63 g, 9.66 mmol) was dissolved in 30 mL
5 N,N-dimethylformamide (DMF), and N-chlorosuccinimide (NCS, 1.29 g, 9.66 mmol) was added. The reaction mixture was stirred at room temperature under nitrogen for 4 hours and concentrated. The residue was partitioned between water and EtOAc and after thorough mixing the aqueous layer was discarded, and the organic layer was washed with saturated $\text{NaCl}_{(aq)}$, dried over magnesium
10 sulfate, filtered and concentrated to an oil. The crude chlorooxime was taken up in 30 mL 1:1 (v/v) water/tetrahydrofuran (THF) and methyl acrylate (1.18 mL, 12.6 mmol) was added, followed by adding sodium bicarbonate (2.46 g, 29.0 mmol). The reaction mixture was stirred at room temperature for 1.5 hours and extracted with EtOAc. The organic extract was dried over magnesium sulfate,
15 filtered, and concentrated. The crude product was purified by flash chromatography (silica gel 60, 230-400 mesh, 3:2 Hexanes/Ethyl acetate) to give **3** (3.19 g, 93%) as a yellow oil: TLC R_f = 0.40 (1:1 hexanes/EtOAc); APCI-MS (m/z): 357 $[M + H]^+$.

Step 4: To a solution of compound of formula **3** (3.10 g, 8.70 mmol) in 30 mL
20 anhydrous THF, cooled to 0°C under nitrogen, is added slowly 26.10 mL (26.10 mmol) 1.0 molar (1.0 M) diisobutylaluminum hydride (DIBAL or DiBALH) solution in cyclohexane (note: effervescence). After addition was complete, the reaction mixture was stirred at 0°C for 1 hour and quenched by slow addition of MeOH. The reaction mixture was partitioned between saturated aqueous
25 potassium sodium tartrate and EtOAc and stirred for 30 minutes. The organic layer was removed, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to a yellow-orange oil which was used without further purification to give **4** (2.76 g, 97%); TLC R_f = 0.13 (1:1 hexanes/EtOAc); APCI-MS (m/z): 329 $[M + H]^+$.

30 **Step 5:** To a solution of triphenylphosphine (3.42 g, 12.98 mmol) in 30 mL MeCN is added under nitrogen carbon tetrabromide (4.29 g, 12.98 mmol),

followed by compound of formula 4 (2.13 g, 6.49 mmol). After stirring at room temperature for 1.5 hours an additional 2.57 g (9.74 mmol) triphenylphosphine and 3.22 g (9.74 mmol) carbon tetrabromide was added, and stirring was continued for 15 minutes. The reaction mixture was concentrated and the crude product was purified by flash chromatography (4:1 Hexanes/Ethyl acetate to 3:2 Hexanes/Ethyl acetate) to give 5 (1.57 g, 62%) as a yellow, crystalline solid: TLC R_f = 0.54 (1:1 hexanes/EtOAc); APCI-MS (m/z): 391 and 393 $[M + H]^+$.

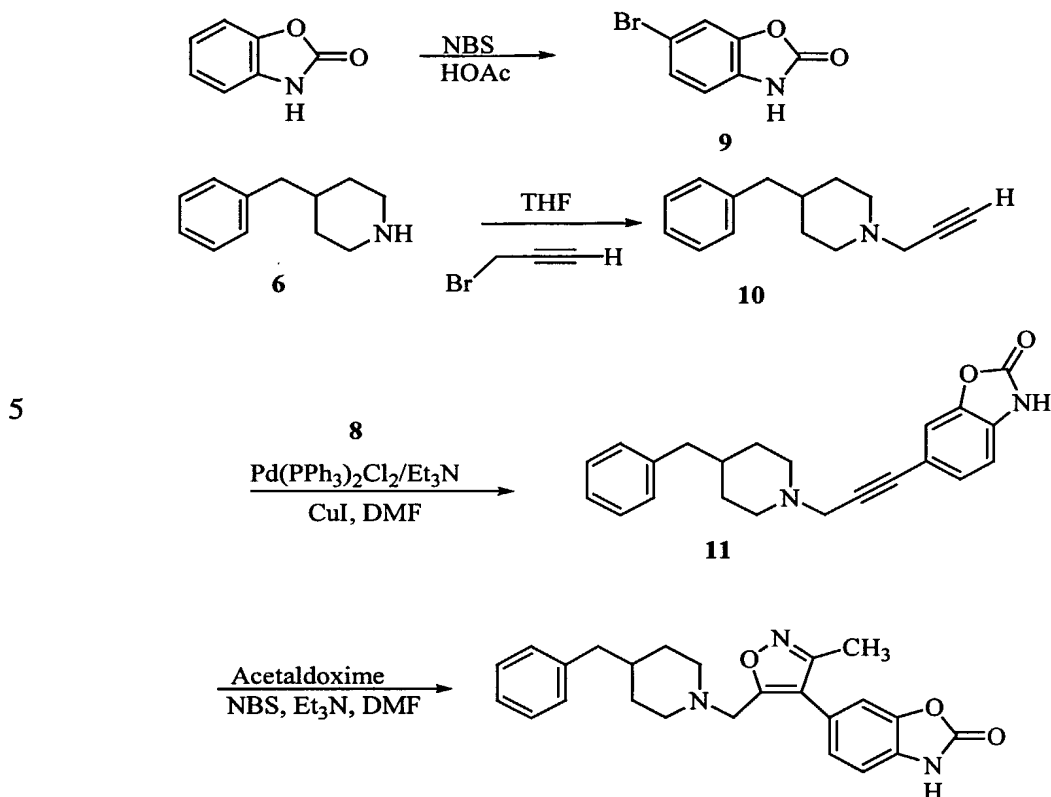
Step 6: A mixture of 4-benzylpiperidine (6) (0.56 mL, 3.26 mmol), compound of formula 5 (1.16 g, 2.96 mmol) and anhydrous potassium carbonate (1.35 g, 9.78 mmol) in 30 mL MeCN was heated at reflux for 24 hours. The reaction mixture was concentrated, and the residue was partitioned between water and EtOAc. The organic layer was washed with water, dried over magnesium sulfate, filtered and concentrated. The crude product was flash chromatographed (EtOAc) to give 7 (1.36 g, 95%) as a yellow oil which crystallized on standing: TLC R_f = 0.36 (EtOAc); APCI-MS (m/z): 486 $[M + H]^+$; Anal. Calcd for $C_{29}H_{31}N_3O_4$: C, 71.73; H, 6.43; N, 8.65. Found: C, 71.70; H, 6.59; N, 8.41.

Step 7: A mixture of compound of formula 7 (410 mg, 0.84 mmol) and 50 mg 20% Pd on C catalyst in 50 mL 1:1 (v/v) MeOH/THF was hydrogenated for 11 hours under a hydrogen pressure of 47.8 psi. The catalyst was filtered off (CELITE), and the filtrate was concentrated to give 8 as a brown, glassy solid; (307 mg (100%): TLC R_f = 0.10 (EtOAc); APCI-MS (m/z): 366 $[M + H]^+$.

Step 8: A mixture of compound of formula 8 (330 mg, 0.90 mmol) and N,N' -carbonyldiimidazole (218 mg, 1.35 mmol) in 10 mL anhydrous THF was refluxed under nitrogen for 1 hour. The reaction mixture was concentrated, and the residue was taken up in EtOAc. The organic layer was washed with water, saturated aqueous NaCl, dried over magnesium sulfate, filtered and concentrated. The crude product was flash chromatographed (3% MeOH in $CHCl_3$ to 5% MeOH in $CHCl_3$) to give 6-[5-(4-benzylpiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3H-benzoxazol-2-one (176 mg, 50%) as an oil which crystallized on standing: (176 mg, 50%): TLC R_f = 0.23 (9:1 $CHCl_3$ /MeOH); APCI-MS (m/z): 392 $[M +$

H]⁺; Anal. Calcd for C₂₃H₂₅N₃O₃: C, 70.57; H, 6.44; N, 10.73. Found C, 70.04; H, 6.52; N, 10.63.

EXAMPLE 2

6-[5-(4-Benzylpiperidin-1-ylmethyl)-3-methylisoxazol-4-yl]-3*H*-benzoxazol-2-one

Step 1: To a solution of benzoxazolinone (20 g, 0.148 mol) in 220 mL glacial acetic acid was added N-bromosuccinimide (NBS, 26.36 g, 0.148 mol), and the reaction mixture was stirred at room temperature for 63 hours before pouring into 1500 mL water. The precipitated product was washed thoroughly with water upon collection and recrystallized from EtOH to give 6-bromo-3*H*-benzoxazol-2-one (9) (25.09 g, 79%): Theory: C, 39.28; H, 1.88; N, 6.54; Br, 37.33. Found: C, 39.36; H, 2.02; N, 6.36; Br, 37.43. MP 192-194°C.

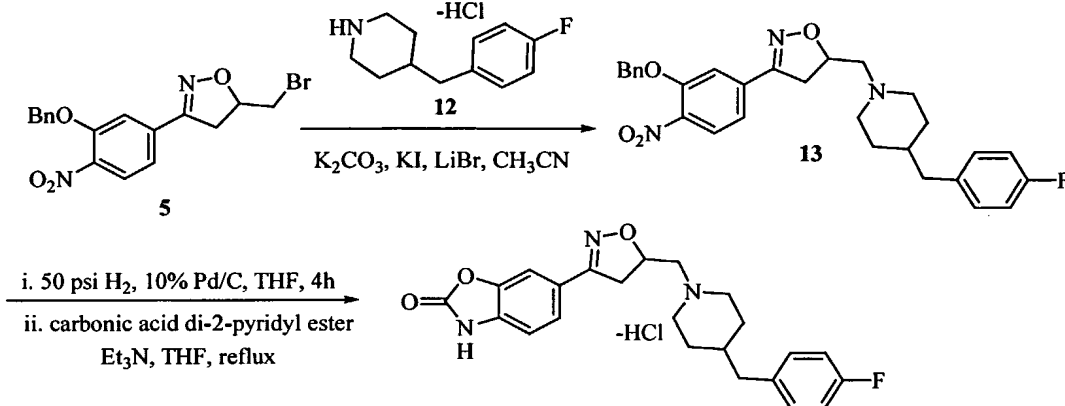
Step 2: A mixture of 4-benzylpiperidine (6) (25 mL, 0.14 mol) and propargyl bromide (10.40 g, 0.07 mol, 80% wt. solution in toluene) in 250 mL anhydrous THF was heated at reflux under nitrogen for 19 hours. The reaction mixture was concentrated, and the residue was taken up in chloroform. The organic layer was

washed with 1.0N aqueous NaOH, dried over magnesium sulfate, filtered and concentrated. The crude product was flash chromatographed (1:1 Hexanes/Ethyl acetate to 3:2 Hexanes/Ethyl acetate) to give **10** (11.90 g, 80%), as an orange oil, MS(APCI) $M + 1 = 214$, TLC (0.34, 1:1 Hexanes/Ethyl acetate; iodine stain).

- 5 **Step 3:** A mixture of compound of formula **10** (7.44 g, 0.0349 mol) and compound of formula **8** (8.19 g, 0.0383 mol) with copper (I) iodide (245 mg, 1.29 mmol), dry triethylamine (14.5 mL, 0.1048 mol), and dichlorobis(triphenylphosphine)palladium(II) (476 mg, 0.68 mmol) in 70 mL anhydrous DMF was heated at 80°C under nitrogen with vigorous stirring for
- 10 18 hours. The reaction mixture was concentrated, and the residue was taken up in acetone and refrigerated for a few hours. The precipitated product was washed with acetone upon collection to give **11** (4.67 g, 39%) as a tan solid, MS(APCI) $M + 1 = 347$, $M - 1 = 345$. Melting point (MP) 235-236°C (dec.), TLC (0.44, EtOAc).
- 15 **Step 4:** To a solution of N-bromosuccinimide (910 mg, 5.11 mmol) in 7.0 mL anhydrous DMF containing 2 drops pyridine was slowly added under nitrogen acetaldoxime (0.32 mL, 5.11 mmol). After addition was complete (5 minutes), the reaction mixture was stirred for 30 minutes at room temperature after which time compound of formula **11** (700 mg, 2.03 mmol) was added in one portion. The
- 20 reaction mixture was heated to 90°C and triethylamine (0.70 mL, 5.11 mmol) was added in one portion. Heating was continued for 24 hours, and the reaction mixture was concentrated. The residue was allowed to stand in a small amount of acetone and over a period of time 212 mg of unreacted compound of formula **11** precipitated and was filtered off. The filtrate was concentrated, and the residue
- 25 was taken up in chloroform. The organic layer was washed with water, dried over magnesium sulfate, filtered and concentrated. The crude product was flash chromatographed (EtOAc) to give 6-[5-(4-benzyl-piperidin-1-ylmethyl)-3-methyl-isoxazol-4-yl]-3*H*-benzoxazol-2-one as an orange oil which solidified on standing, 100 mg (12%), MS(APCI) $M + 1 = 404$, $M - 1 = 402$. Theory: C, 71.44; H, 6.25; N, 10.41. Found: C, 68.81; H, 6.20; N, 10.07. HPLC (C-18, 1:1
- 30 Water/Acetonitrile, isocratic) retention time (RT) = 15.34 min (93.8%).

EXAMPLE 3

6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one hydrochloride

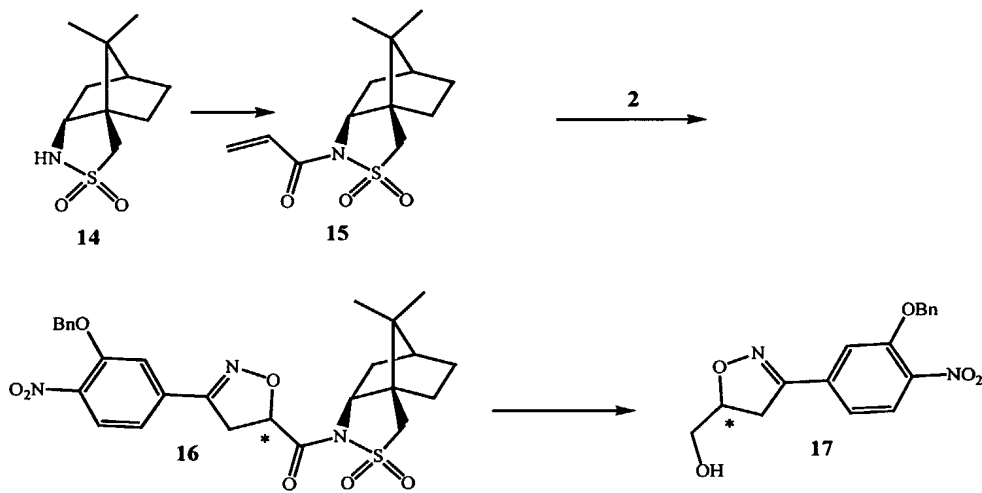


- 5 Step 1:** To a solution of bromide of formula 5 (2.84 g, 7.26 mmol) and amine of formula 12 (1.67 g, 7.26 mmol) in THF (25 mL) was added K_2CO_3 (2.25 g, 16.3 mmol), KI (120 mg, 0.726 mmol), and LiBr (150 mg, 1.72 mmol). The mixture was warmed to 50°C overnight (*ca.* 12 hours). After cooling to ambient temperature, the reaction solvent was removed under reduced pressure. The residue was partitioned between water and ethyl acetate. Warming was necessary to form a homogenous organic layer. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give amine of formula 13 as a yellow residue. Purification by chromatography (silica, 1:99 to 5:95 MeOH/ CH_2Cl_2) gave amine of formula 13 (2.36 g, 65%) as a pale yellow solid.
- 15 Step 2:** To a solution of amine of formula 13 (1.25 g, 2.48 mmol) in THF (80 mL) was added 10% Pd/C (200 mg). The mixture was shaken under 50 pounds per square inch (psi) of H_2 for 4 hours then rapidly filtered through CELITE under reduced pressure into a round bottom flask. The flask was capped with a septum and purged with nitrogen. To the clear solution was added carbonic acid di-2-pyridyl ester (590 mg, 2.78 mmol) and Et_3N (800 μ L, 5.45 mmol). The solution was refluxed overnight (*ca.* 12 hours). Although no change in R_F (TLC: 1:9 MeOH/ CH_2Cl_2 , R_F = 0.22) was observed, a color change from green to red was observed using ninhydrin that distinguished the starting material from the product. The solvent was removed under reduced pressure to afford a yellow
- 20**

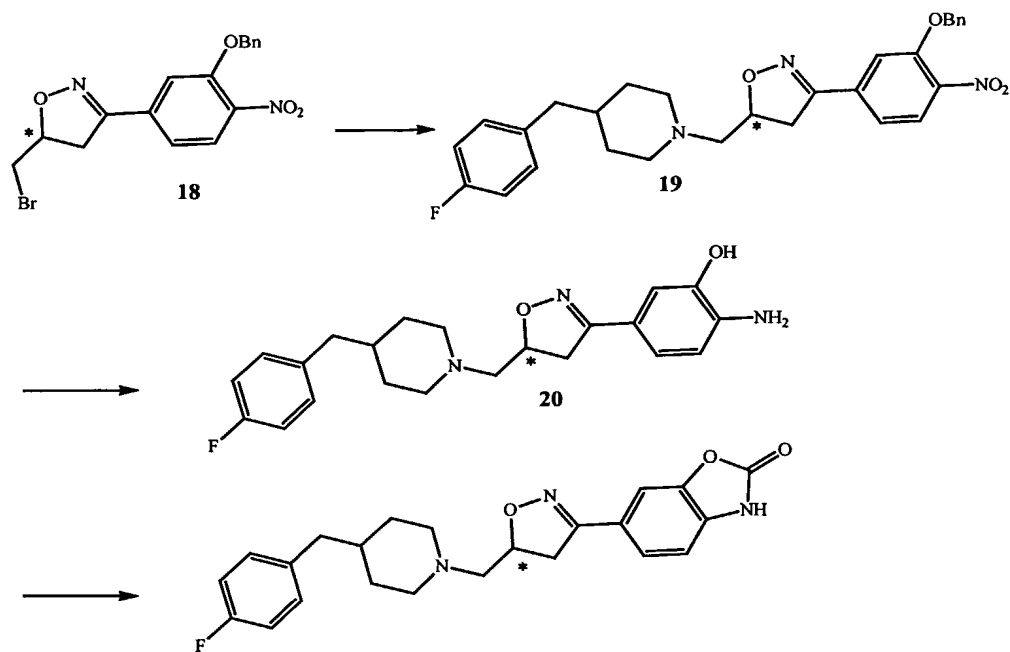
residue. Purification by chromatography (silica gel, 1:99 to 5:95 MeOH/CH₂Cl₂) gave a yellow product. The colored product was taken up in MeOH and the solution acidified with 1 M HCl/Et₂O. This solution was dripped into 200 mL of Et₂O. The resulting suspension was briefly sonicated, and then the solid was
5 collected by filtration to give (±)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one hydrochloride (728 mg, 66%) as a white solid.

EXAMPLES 4(a) AND 4(b)

4(a): (+)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one
10 yl}-3*H*-benzoxazol-2-one



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Step 1: Washed (heptane) NaH (1.45 g, 36.3 mmol, 60% in mineral oil) in toluene (150 mL) was treated with the (1*R*)-sultam **14** (5.20 g, 24.2 mmol) at room temperature under N₂. After stirring at room temperature for 1.5 hours, Cu^ICl (239 mg, 2.42 mmol) was added followed by acryloyl chloride (4.38 g, 4.84 mmol, 3.93 mL). After stirring for 3 hours at room temperature, the reaction was quenched with H₂O (1 mL) and the solvents removed. The mixture was taken up in EtOAc and passed through a 'plug' (~20 g) of silica gel, and the EtOAc removed. The product was purified by chromatography (CH₂Cl₂) to yield compound **15** as a white solid (3.92 g, 60%).

See *J. Org. Chem.*, 1990;**55**:4585 for spectral data

R_f (EtOAc/C₇) – 0.62

R_f (2% MeOH/CH₂Cl₂) – 0.50.

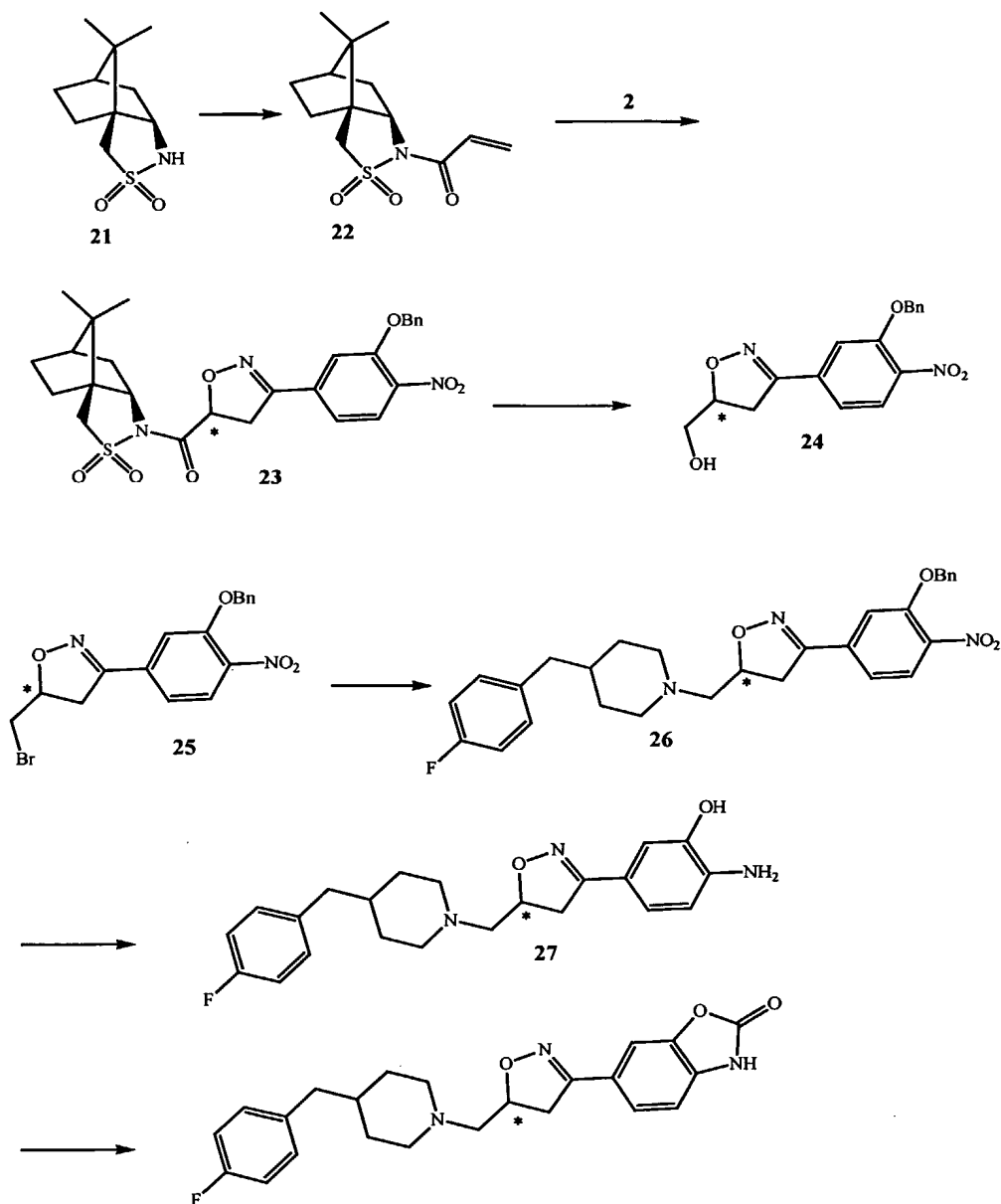
Step 2: The oxime **15** (3.86 g, 14.20 mmol) and NCS (1.90 g, 14.2 mmol) were stirred in DMF (75 mL) for 3 hours at room temperature. The DMF was removed and the product taken up in EtOAc, washed with brine and dried (MgSO₄). After removal of the solvent the material was taken up in THF/H₂O (100:100 mL) and the sultam (IIa, 3.82 g, 14.20 mmol) and NaHCO₃ (3.78, 45 mmol) were added.

After 1 hour the mixture was diluted with EtOAc, washed with H₂O, brine and dried (MgSO₄). The crude material obtained was purified by recrystallization (EtOAc) to afford compound **16** as a very pale yellow 'fluffy' crystals (5.17 g, 68% from 3 crops of crystals).

- 5 Product from (1R)-sultam $[\alpha]_D^{23} = +224^\circ$ (c=0.30, MeCN)
m/z 540.0 (MH⁺),
 ν_{\max} 2761, 1698, 1519, 1338, 1273, 849, 737 cm⁻¹,
 δ_H 1.00 (3H, s, CH₃), 1.22 (3H, s, CH₃), 1.40 (2H, m, CH₂), 1.92 (3H, m, alkyl),
2.10 (1H, dd, CH, *J* 8.0, 13.6 Hz), 2.20 (1H, dd, CH, *J* 3.6, 13.6 Hz), 3.48 (1H, d,
10 CHHSO₂, *J* 14.0 Hz), 3.59 (1H, dd, CHH, *J* 11.2, 17.2 Hz), 3.59 (1H, d,
CHHSO₂, *J* 13.6 Hz), 3.71 (1H, dd, CHN, *J* 6.8, 17.2 Hz), 5.26 (2H, s, OCH₂),
5.76 (1H, dd, CHN, *J* 6.8, 11.2 Hz), 7.18 (1H, dd, aromatic (arom.) *J* 1.6, 8.4 Hz),
7.32-7.48 (5H, m, Ph), 7.58 (1H, d, arom., *J* 1.2 Hz), 7.88 (1H, d. arom., *J* 7.6
Hz).
- 15 **Step 3:** DiBALH reduction of compound **16** as in Example 1, Step 4; and
purification by chromatography (0-70% EtOAc/C₇) gave **17** (2.19 g, 71%).
Step 4: Bromination of compound **17** as in Example 1, Step 5 gave **18**.
Step 5: Coupling of compound **18** as in Example 1, Step 6 gave **19**: $[\alpha]_D^{24} =$
 $+57^\circ$ (c=0.42, CH₂Cl₂).
- 20 **Step 6:** Reduction of compound **19** as in Example 1, 7 gave **20**.
Step 7: Benzoxazol-2-one ring formation of compound **20** as in Example 1, Step 8
gave (+)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-
yl}-3*H*-benzoxazol-2-one: $[\alpha]_D^{24} = +102^\circ$ (c=0.31, MeOH).

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Example 4(b): (-)-6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one



5 Step 1: Compound **22** was prepared in a manner similar to Example 4a, Step 1, except (1*S*)-sultam (**21**) was used in place of the (1*R*)-sultam.

Step 2: Compound **23** was prepared in a manner similar to Example 4a, Step 2: $[\alpha]_D^{23} = -224^\circ$ ($c=0.27$, MeCN).

Step 3: DiBALH reduction of compound **23** as in Example 1, Step 4 gave **24**.

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Step 4: Bromination of compound **24** as in Example 1, Step 5 gave **25**.

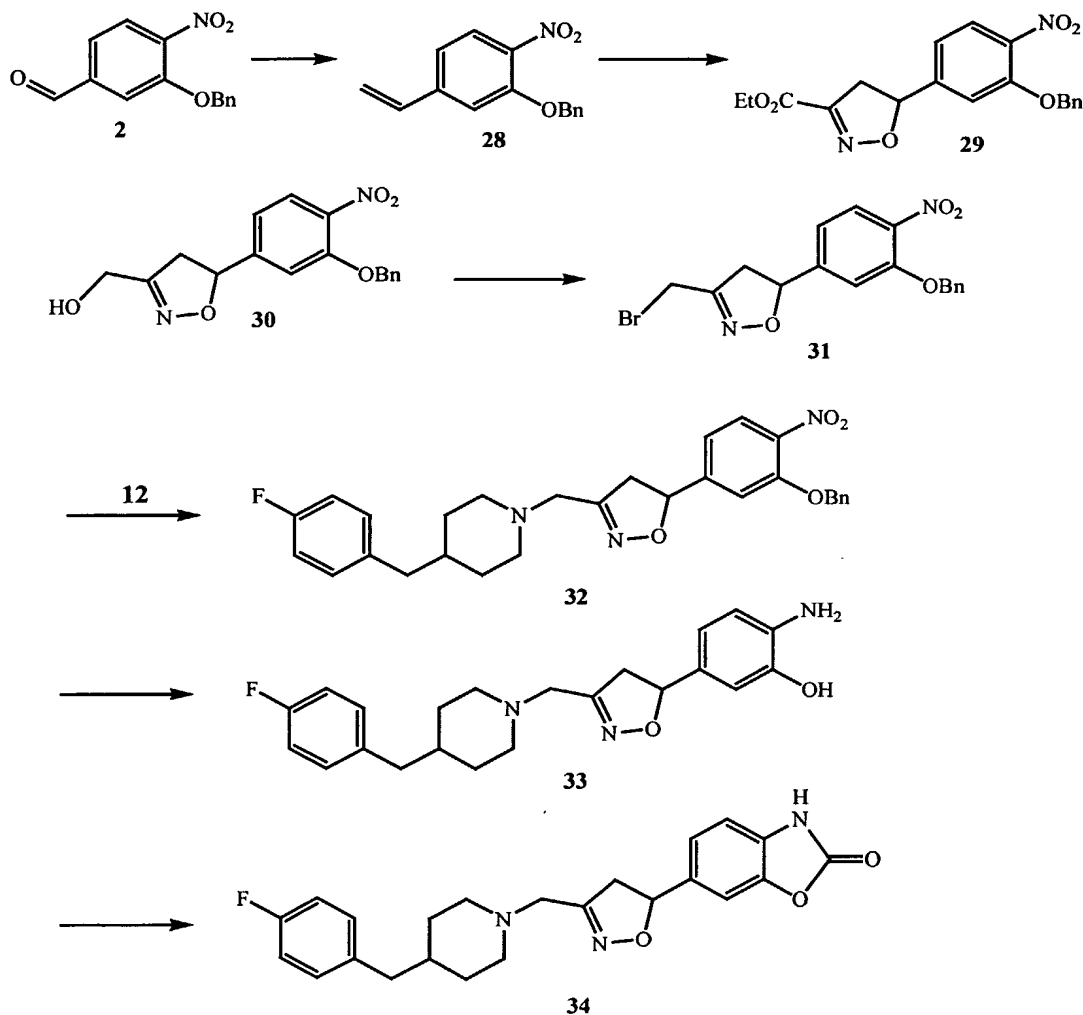
Step 5: Coupling of compound **25** as in Example 1, Step 6 gave **26**: $[\alpha]_D^{24} = -69^\circ$ ($c=0.46$, CH_2Cl_2).

Step 6: Reduction of compound **26** as in Example 1, Step 7 gave **27**.

Step 7: Benzoxazol-2-one ring formation of compound **27** as in Example 1, Step 8 gave (-)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one: $[\alpha]_D^{23} = -105^\circ$ ($c=0.44$, MeOH).

EXAMPLE 5

6-{3-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-5-yl}-3*H*-benzoxazol-2-one



Step 1: Butyllithium (16.0 mL, 40 mmol, 2.5 M in hexanes) was added to a suspension of methyltriphenylphosphonium bromide (12.50 g, 35.0 mmol) in THF (300 mL at 0°C. After stirring for 1 hour, a solution of **2** (7.72 g, 30.04 mmol) was added, and the mixture stirred at room temperature for 3 hours. The solvent was removed, and the crude material was taken up in EtOAc and triturated with heptane, the solids were filtered off ($\times 5$). The filtrate was then purified by chromatography (0-10% EtOAc in heptane) to give **28** as a yellow oil (3.04 g, 40%).

m/z 254.09 (M-H⁻)

ν_{\max} 1601, 1585, 1514, 1345 cm⁻¹

δ_{H} 5.26 (2H, s, CH₂O), 5.45 (1H, d, CH=, J 10.4 Hz), 5/82 (1H, d, CH=, J 17.6 Hz), 6.68 (1H, dd, dd, CH=, J 10.8, 17.6 Hz), 7.07 (1H, dd, arom., J 1.6, 8.4 Hz), 7.11 (1H, s, arom.), 7.34 (1H, m, arom.), 7.39 (2H, m, arom.), 7.48 (2H, m, arom.), 7.88 (1H, d, arom., J 8.4 Hz).

Step 2: Compound **28** (1.50 g, 5.88 mmol), ethyl 2-chloro-2-(hydroxyimino)acetate (888 mg, 5.88 mmol), NaHCO₃ (988 mg, 11.76 mmol) were stirred at room temperature in THF/H₂O (10/5 mL). After 1 hour a further aliquot (888 mg, 5.88 mmol) of ethyl 2-chloro-2-(hydroxyimino)acetate was added, and stirring continued for a further 1 hour. The mixture was then diluted with EtOAc, washed with brine and dried (MgSO₄). Purification by chromatography (0-40% EtOAc in heptane) gave **29** as a yellow oil which solidified on standing (1.91 g, 88%).

m/z 371.15 (MH⁺)

ν_{\max} 1722, 1609, 1593, 1519, 1251 cm⁻¹

δ_{H} 1.39 (3H, t, CH₃, J 7.2 Hz), 3.12 (1H, dd, CHH, J 8.0, 18.0 Hz), 3.70 (1H, dd, CHH, J 12.0, 17.6 Hz), 4.37 (2H, q, CH₂, J 7.2 Hz), 5.25 (2H, s, CH₂O), 5.80 (1H, dd, CH, J 8.0, 11.6 Hz), 6.94 (1H, dd, arom., J 1.2, 8.0 Hz), 7.12 (1H, s, arom.), 7.32-7.47 (5H, m, Ph), 7.88 (1H, d, arom., J 8.0 Hz).

Step 3: DiBALH (12.90 mL, 12.90 mmol, 1 M in THF) was added to a solution of

29 (1.91 g, 5.16 mmol) in THF (50 mL) at 0°C. After 1 hour a further aliquot of

DiBALH (6.50 mL, 6.50 mmol, 1 M in THF) was added and the mixture stirred for another 1 hour. MeOH (1 mL) was added followed by saturated NaHCO₃ (20 mL) and the mixture stirred for 20 minutes. The solids were filtered off and the filtrate taken up in EtOAc, washed with brine and dried (MgSO₄). The material was

- 5 purified by chromatography (0-50% EtOAc in heptane) to give **30** as a straw colored oil (66 mg, 39%).

m/z 329.21 (MH⁺)

ν_{\max} 3390, 1609, 1519, 1352 cm⁻¹

- δ_{H} 1.84 (1H, t, OH, 6.0 Hz), 2.93 (1H, dd, CHH, J 7.2, 17.2 Hz), 3.54 (1H, dd,
10 CHH, J 11.2, 17.2 Hz), 4.43 (2H, d, CH₂OH, J 6.0 Hz), 5.26 (2H, d, CH₂O, J 3.6 Hz), 5.65 (1H, dd, CH, J 7.2, 11.2 Hz), 6.93 (1H, dd, arom., J 1.2, 8.0 Hz), 7.15 (1H, d, arom., J 1.2 Hz), 7.32-7.48 (5H, m, Ph), 7.86 (1H, d, arom., J 8.0 Hz).

- Step 4:** Triphenylphosphine (799 mg, 3.05 mmol) and carbontetrabromide (1.01 g, 3.05 mmol) were added to a solution of **30** (667 mg, 2.03 mmol) in MeCN (20
15 mL) and the resulting mixture stirred at room temperature for 2 hours. The solvent was removed and the crude material purified by chromatography (0-50% EtOAc in heptane) to **31** as a yellow oil (719 mg, 90%).

m/z 393.11/391.11 (MH⁺)

ν_{\max} 1608, 1519, 1350 cm⁻¹

- δ_{H} 3.00 (1H, dd, CHH, J 7.2, 17.2 Hz), 3.60 (1H, dd, CHH, J 11.2, 17.2 Hz), 4.18
20 (2H, s, CH₂Br), 5.25 (2H, s, CH₂O), 5.68 (1H, dd, CH, J 7.6, 11.2 Hz), 6.94 (1H, d, arom., J 8.4 Hz), 7.13 (1H, s, arom.), 7.32-7.47 (5H, m, Ph), 7.87 (1H, d, arom., J 8.0 Hz).

- Step 5:** Compound **31** (7.15 mg, 1.83 mmol), 4-(4-fluorobenzyl)piperidine
25 hydrochloride (**12**) (504 mg, 2.19 mmol) and anhydrous K₂CO₃ (507 mg, 3.66 mmol) in MeCN (10 mL) were stirred and heated to reflux for 16 hours. The solution was then diluted with EtOAc, washed with brine and dried (MgSO₄). The product was purified by chromatography (0-70% EtOAc in heptane) to yield **32** as a yellow oil (662 mg, 72%).

m/z 504.26 (MH^+)

ν_{\max} 2902, 1608, 1509, 850 cm^{-1}

δ_H 1.89 (2H, m, alkyl), 1.45 (1H, m, alkyl), 1.60 (2H, m, alkyl), 1.97 (2H, m, alkyl), 2.47 (2H, d, ArCH_2 , J 7.2 Hz), 2.67 (1H, d, CH, J 11.2 Hz), 2.80 (1H, d, CH, J 10.8 Hz), 2.90 (1H, dd, CHH, J 7.2, 17.2 Hz), 3.21 (2H, dd, CH_2N , J 14.0, 22.0 Hz), 3.49 (1H, dd, CHH, J 11.2, 17.2 Hz), 5.22 (2H, dd, CH_2O , J 12.0, 16.0 Hz), 5.59 (1H, dd, CH, J 7.2, 11.2 Hz), 6.95 (3H, m, arom.), 7.06 (2H, m, arom.), 7.15 (1H, s, arom.), 7.31-7.47 (5H, m, Ph), 7.86 (1H, d, arom., J 8.0 Hz).

Step 6: Compound **32** (595 mg, 1.38 mmol) and Pd-C (10%, 150 mg) in MeOH (100 mL) were (in two batches) subjected to hydrogenation at 50 psi and 30°C for 1 hour. The catalyst was removed by filtration through a 'filter aid' and yielded **33** as an orange colored glass upon removal of the solvent (490 mg, 90%).

m/z 383.18 (MH^+)

ν_{\max} 3370, 2923, 1509, 1219 cm^{-1}

δ_H 1.25 (2H, bm, alkyl), 1.60 (4H, m, alkyl, NH_2), 1.98 (1H, m, alkyl), 2.48 (2H, d, ArCH_2 , J 6.8 Hz), 2.83 (2H, m, alkyl), 2.94 (1H, dd, CHH, J 8.8, 17.6 Hz), 3.23 (2H, s, CH_2N), 3.32 (1H, dd, CHH, J 10.8, 17.2 Hz), 3.67 (1H, bs, OH), 5.42 (1H, dd, CH, J 8.8, 10.8 Hz), 6.70 (2H, s, arom.), 6.73 (1H, s, arom.), 6.96 (1H, s, arom.), 7.06 (2H, m, arom.).

Step 7: Compound **33** (490 mg, 1.28 mmol) and carbonyldiimidazole (CDI) (311 mg, 1.92 mmol) in THF (20 mL) were heated to reflux for 1 hour. The mixture was diluted with EtOAc, washed with brine and dried (MgSO_4). The compound was purified by chromatography (0-4% MeOH in CH_2Cl_2) and repeated (0-100% EtOAc in heptane) to yield 6-{3-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-5-yl}-3*H*-benzoxazol-2-one as a yellow foam (220 mg, 42%).

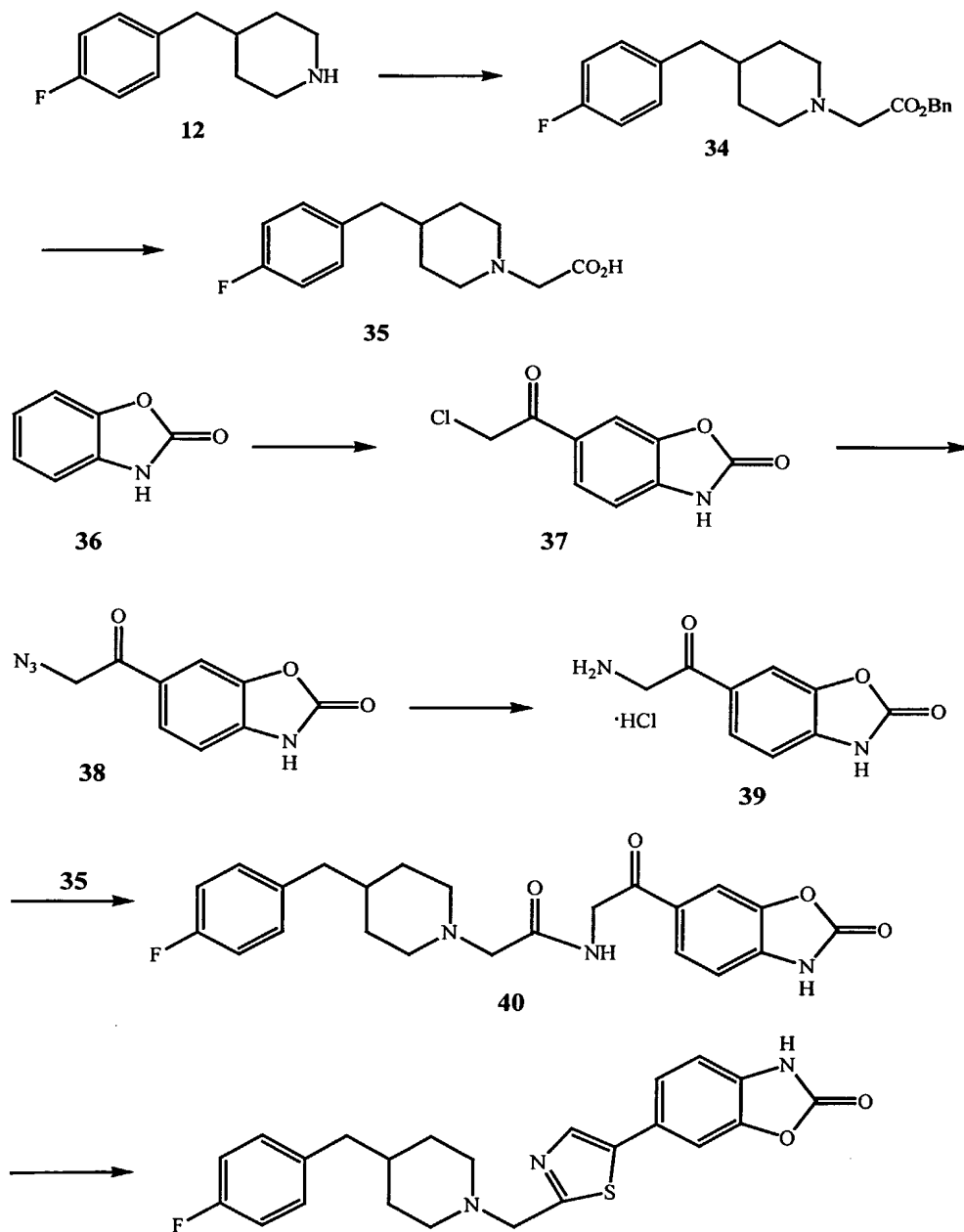
m/z 410.20 (MH^+)

ν_{\max} 1776, 1509, 1219 cm^{-1}

δ_H 1.26 (2H, bm, alkyl), 1.43-1.65 (3H, m, alkyl), 1.98 (1H, m, alkyl), 2.48 (2H, d, ArCH_2 , J 7.2 Hz), 2.75 (1H, d, CHH, J 11.6 Hz), 2.84 (1H, dd, CHH, J 10.8

Hz), 2.96 (1H, dd, CHH, J 8.0, 17.6 Hz), 3.23 (2H, s, CH₂N), 3.24 (2H, s, CH₂N), 3.44 (1H, dd, CHH, J 10.8, 17.2 Hz), 5.58 (1H, dd, CH, J 8.0, 10.8 Hz), 6.93-7.16 (6H, m, arom.), 7.20 (1H, s, arom.), 7.99 (1H, bs, NH).

EXAMPLE 6

5 6-{2-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3*H*-benzoxazol-2-one

Step 1: To a stirring solution of 4-(4-fluorobenzyl)piperidine (12) (10.0 g, 51.744 mmol) in dichloromethane (10 mL) at 0°C was added triethylamine

- (7.21 mL, 51.744 mmol), followed by benzyl-2-bromoacetate (8.20 mL, 51.744 mmol). The resulting solution was allowed to warm to room temperature stirring for 20 hours, then heated to 30°C for a further 6.5 hours. The reaction mixture was evaporated to dryness *in vacuo* to give a yellow gum. This was
- 5 adsorbed onto silica gel, and subjected to column chromatography [EtOAc/Heptane (1:10)] to give **34** (5.07 g, 29%) as a colorless oil:
- m/z (APCI+) 342 (MH^+ , 100%),
- δ_H 1.36 (2H, t, J 6.8), 1.25 (2H, t, J 3.6 Hz), 1.36 (2H, dt, J 3.6 Hz), 1.50 (1H, m), 1.60 (2H, d, J 12.4 Hz), 2.10 (2H, dt, J 2.4, 12 Hz), 2.49 (2H, d, J 6.8 Hz),
- 10 2.89 (2H, d, J 11.2 Hz), 3.20 (2H, s, $N-CH_2-CO$), 5.14 (2H, s, OCH_2Ph), 6.94 (2H, t, J 8.4 Hz), 7.05 (2H, dt, J 2 and 5.2 Hz), 7.32-7.35 (5H, m).
- HPLC R_t = 1.73 min; 69.5%; (5-100% MeCN in H_2O (both +0.1% trifluoroacetic acid) over 2.5 minutes at 3 mL/min, held at 100% MeCN for 0.5 minute; Prodigy ODS III 5 μ , 50 \times 4.6 mm).
- 15 **Step 2:** To a solution of **34** (5.07 g, 14.85 mmol) in methanol (60 mL) was added 5% palladium on activated carbon (2.50 g, 50% by wgt.) and hydrogenated at 48 psi/25°C for 15 hours. The reaction mixture was then filtered through CELITE, the catalyst washed with methanol (3 \times 25 mL) and the filtrate condensed to dryness *in vacuo* to give a pale yellow solid. The solid was subject to column
- 20 chromatography [MeOH/DCM (1:9)] to give **35** (1.70, 46.6%) as a colorless solid:
- m/z (APCI+) 252 (MH^+ , 100%) and 266 ($[M+MeOH]^+$, 50%),
- m/z (APCI-) 250 ($[M-H]^-$, 100%).
- ν_{max} (KBr) 1608 (C=O), 1502s, 1379s cm^{-1}
- δ_H 1.71 (1H, m), 1.78 (2H, m), 2.58 (2H, d, J 6.4 Hz), 2.72 (2H, m), 3.48 (2H, d, J 4.8 Hz), 3.68 (2H, d, J 12.0 Hz), 4.1 (1H, s, OH), 6.95 (2H, t, J 8.6 Hz), 7.07
- 25 (2H, dt, J 2.0, 5.6 Hz),
- HPLC R_t = 1.36 min; 100%; (5-100% MeCN in H_2O (both +0.1% trifluoroacetic acid) over 2.5 minutes at 3 mL/minute, held at 100% MeCN for 0.5 minute; Prodigy ODS III 5 μ , 50 \times 4.6 mm).

Step 3: To a stirred slurry of aluminum trichloride (49.34 g, 370.05 mmol) in 1,2-dichloroethane (150 mL) at 0°C under nitrogen was added chloroacetyl chloride (33.43 g, 23.58 mL, 296.04 mmol) dropwise over 30 minutes. After 1 hour, a suspension of 2-benzoxalinone (**36**) (20.0 g, 148.02 mmol) in 1,2-dichloroethane (50 mL) was added over 30 minutes. The resulting suspension was stirred at 0°C for 2.5 hours, then heated to 50°C for 20 hours. The mixture was then poured onto crushed ice, stirred for 30 minutes, and the resulting mixture filtered. The residue was dried *in vacuo* at 60°C for 3 days to give **37** as a pale brown solid (13.70 g, 43%).

δ_{H} (d_6 -Me₂SO) 5.16 (2H, s, CH₂Cl), 7.23 (1H, d, arom., *J* 8.0 Hz) 7.84 (1H, dd, arom., *J* 1.5, 8.0 Hz) 7.88 (1H, s, arom.)
HPLC retention time (*R*_t) = 1.53 min; 79.71%; (5-100% MeCN in H₂O (both +0.1% trifluoroacetic acid) over 2.5 minutes at 3 mL/min, held at 100% MeCN for 0.5 minute; Prodigy ODS III 5 μ , 50 \times 4.6 mm.

Step 4: To a stirred solution of **37** (6.00 g, 28.4 mmol) in DMF (60 mL) was added sodium azide (1.85 g, 28.5 mmol). After 3 hours, the DMF was removed under reduced pressure to give a solid which was washed well with water, filtered and dried to yield **38** as a brown solid (4.5 g, 73%).

m/z 217.09 (M-H⁻)

ν_{max} 3405, 2921, 2135, 1770, 1660, 1606, 1442, 1268, 1240, 1190, 920 cm⁻¹
 δ_{H} (DMSO) 4.86 (2H, s, CH₂), 7.22 (1H, d, arom., *J* 8.1 Hz), 7.79-7.82 (1H, m, arom.), 7.83 (1H, s, arom.) NH not seen.

Step 5: A solution of **38** (100 mg, 0.46 mmol) and Pd-C (5%, 15 mg) in methanol (20 mL) and concentrated HCl (6 drops) was subjected to hydrogenation at 10 psi and 25°C for 25 minutes. The catalyst was removed by filtration through a 'filter aid' and the solvent removed to give **39** (85 mg, 81%) as a pale brown solid.

m/z 192.97 (MH⁺)

ν_{max} 3374, 2967, 1767, 1695, 1623, 1495, 1419, 1268, 1149 cm⁻¹

δ_{H} (DMSO) 4.56 (2H, s, CH_2), 7.27 (1H, d, arom., J 8.3 Hz), 7.89 (1H, d, arom., J 8.1 Hz), 7.93 (1H, s, arom.), 8.34 (3H, s, NH_3^+), 12.34 (1H, s, NH).

Step 6: To a stirring solution of **35** (2.43 g, 9.68 mmol) in dimethylformamide (50 mL) was added *N,N*-diisopropylethylamine (DIPEA) (3.37 g, 19.36 mmol) followed by *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) (3.67 g, 9.68 mmol). After 45 minutes, **39** (1.86 g, 9.68 mmol) was added, and the resulting solution stirred at room temperature for 3 hours. The reaction mixture was condensed to dryness *in vacuo*, redissolved in EtOAc, and washed with saturated aqueous sodium bicarbonate solution. A precipitate formed in the partition, this was filtered and dried. The organic phase was then was then dried with magnesium sulfate and condensed to dryness *in vacuo*. The resulting brown oil and the filtered solid were combined, adsorbed onto silica gel, and subject to column chromatography [MeOH/DCM (0-5% MeOH over 60 minutes)] to give **40** (0.493 g, 12%) as a tan solid:

ν_{max} (KBr) 3401w, 3079w, 1777s, 1675w, 1621s, 1510m, 1451m, 1270s, 947m, 844s.

NMR δ_{H} (DMSO- d_6) 1.45 (2H, dd, J 11.2 Hz), 1.70 (3H, m), 2.53 (2H, d, J 5.5 Hz) 2.94 (2H, m), 3.37 (4H, m), 3.93 (2H, s), 4.41 (4H, s), 4.73 (2H, d, J 5.6 Hz), 7.12-7.17 (2H, t, arom., J 8.8 Hz), 7.21 (3H, m, arom.), 7.87-7.97 (2H, m, arom.), 8.85 (1H, brs, amide NH),

m/z (APCI+) 426 (MH^+ , 100%), 251 (Acid^+ , 25%)

m/z (APCI-) 424 ($[\text{M}-\text{H}]^-$, 100%).

Step 7: Purified by preparative HPLC (10-100% ACN (0.1% TFA) over 30 minutes, held at 100% for 5 minutes at 20 mL/min, YMC-PACK ODS-A, 5 micron, 100 \times 30 mm, 254 nm) to give 6-{2-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3*H*-benzoxazol-2-one (0.031 g, 6%) as a yellow solid:

ν_{max} (KBr) 3420br, 3124br, 2921ms, 1613w, 1511w, 1466s (C(S)NH), 1333ms (NC(S)N), 1190s, 807ws,

m/z (APCI+) 421 (MH^+ , 100%), 248 (10%)

m/z (APCI-) 419 ($[\text{M}-\text{H}]^-$, 100%), 246 (10%),

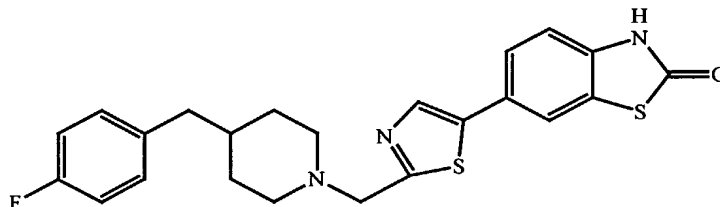
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NMR δ_H (DMSO- d_6) 1.23 (2H, m), 1.51 (1H, m), 1.54 (2H, d, J 12.2 Hz), 2.04 (2H, t, J 11.0 Hz), 2.88 (2H, d, J 11.2 Hz), 3.26 (2H, d, J 10.0 Hz), 3.75 (2H, s), 7.15 (4H, d, arom., J 8.0 Hz), 7.25 (3H, t, arom., J 8.3 Hz), 7.40 (1H, d, arom., J 8.3 Hz), 8.0 (1H, s, arom.)

- 5 HPLC R_t = 5.94 minutes, 97.48% (20% to 100% ACN (0.1% TFA) in 20 minutes, held at 100% ACN for 1 minute at 1.5 mL/min, 40°C liquid chromatography-mass spectrometry (LC-MS) Prodigy ODS(3), 3 micron, 150 \times 4.6 mm 250 nm.

EXAMPLE 7

- 10 6-{2-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3*H*-benzothiazol-2-one



- Step 1:** Treatment of 2-hydroxybenzothiazole with chloroacetyl chloride and aluminum trichloride, following the procedure described in Example 6, Step 3, gave 6-(2-chloroethanoyl)-3*H*-benzothiazol-2-one: δ_H (d_6 -Me₂SO) 5.14 (2H, s, CH₂Cl), 7.23 (1H, d, arom., J 8.5 Hz), 7.92 (1H, dd, arom., J 9.0, 2.0 Hz), 8.27 (1H, d, arom., J 1.5 Hz) and 12.34 (1H, s, NH):

m/z (APCI-) 228 and 226 (each $[M-H]^-$, 25 and 55%).

- Step 2:** Treatment of 6-(2-chloroethanoyl)-3*H*-benzothiazol-2-one with sodium azide, following the procedure described in Example 6, Step 4, gave 6-(2-azidoethanoyl)-3*H*-benzothiazol-2-one (6.95 g, 96%):

m/z 233.08 ($M-H^-$)

ν_{max} 3441, 2117, 1676, 1595, 1399, 1343, 1269, 1214, 1067 cm^{-1}

δ_H (DMSO) 4.84 (2H, s, CH₂), 7.23 (1H, d, arom., J 8.3 Hz), 7.85-7.88 (1H, m, arom.), 8.20 (1H, s, arom.), NH not seen; and

- 25 **Step 3:** 6-(2-Azidoethanoyl)-3*H*-benzothiazol-2-one (0.5 g, 2.14 mmol) and Pd-C (5%, 0.17 g) in methanol (40 mL) and concentrated HCl (0.5 mL) were subjected

to hydrogenation at 20 psi and 25°C for 1 hour. The catalyst was removed by filtration through a 'filter aid' and the solvent removed to give 6-(2-aminoethanoyl)-3*H*-benzothiazol-2-one hydrochloride as a light brown solid (0.5 g, 96%).

5 m/z 209.04 (MH^+)

ν_{\max} 3405, 2958, 1681, 1642, 1591, 1222, 1179, 814 cm^{-1}

δ_H (DMSO) 4.53 (2H, s, CH_2), 7.31 (1H, d, arom., J 8.5 Hz), 7.94-7.97 (1H, m, arom.), 8.33 (1H, s, arom.), 8.43 (3H, s, NH_3^+), 12.61 (1H, s, NH).

Step 4: Coupling of 6-(2-aminoethanoyl)-3*H*-benzothiazol-2-one hydrochloride

10 with **35** following the procedure described in Example 6, Step 6, gave 2-[4-(4-fluorobenzyl)piperidin-1-yl]-*N*-[2-oxo-2-(2-oxo-2,3-dihydrobenzothiazol-6-yl)ethyl]acetamide:

ν_{\max} (KBr) 3404m, 3346m, 4047, 1708s (ketone $\text{C}=\text{O}$), 1681s and 1653s ($2 \times$ amide $\text{C}=\text{O}$), 1596m, 1508m, 1218m and 841s cm^{-1}

15 NMR δ_H (DMSO- d_6) 1.40-1.60 (2H, m), 1.71-1.80 (3H, m), 2.97-2.99 (2H, m), 3.45 (2H, d, J 11 Hz, $\text{CH}_2\text{C}_6\text{H}_4\text{F}$), 3.98 [2H, s, $\text{C}(\text{O})\text{CH}_2\text{N}$], 4.73 [2H, d, J 5 Hz, $\text{C}(\text{O})\text{CH}_2\text{NH}$], 7.10 (2H, t, J 8.5 Hz), 7.21-7.24 (3H, m), 7.93 (1H, dd, J 8 and 1 Hz), 8.31 (1H, d, J 1 Hz), 8.90 (1H, brs), 9.57 (1H, brs) and 12.43 (1H, brs), m/z (APCI+) 442 (MH^+ , 100%),

20 m/z (APCI-) 440 ($[M-H]^-$, 50%) and 413 (100),

HPLC R_t = 8.98 min; 97.24%; (20-100% MeCN in H_2O (both +0.1% trifluoroacetic acid) over 15 minutes at 1 mL/min, held at 100% MeCN for 5 minutes; Prodigy ODS III 5 μ , 250 \times 4.6 mm, 40°C).

Step 5: To a stirred solution of 2-[4-(4-fluorobenzyl)piperidin-1-yl]-*N*-[2-oxo-2-

25 (2-oxo-2,3-dihydrobenzothiazol-6-yl)ethyl]acetamide (0.50 g, 1.13 mmol) in 1,4-dioxan (30 mL) was added [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (Lawesson's reagent) (0.69 g, 1.70 mmol). The resulting suspension was heated at reflux for 24 hours. The reaction mixture was condensed to dryness *in vacuo*, redissolved in EtOAc, and washed with saturated

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aqueous sodium hydrogen carbonate, and saturated brine. The organic phase was dried (MgSO₄) and condensed to dryness *in vacuo*. The material was then subject to column chromatography [silica gel, EtOAc/Heptanes (0-50% EtOAc over 60 min)] gave 6-{2-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3H-benzothiazol-2-one (0.087 g, 18%) as an off-white solid:

5 ν_{max} (KBr) 2918ms, 2852m, 1681s (ketone C=O), 1599m, 1507s, 1454ms, 1214m, 1214ms, 804ms,

m/z (APCI+) 440 (MH⁺, 100%), 249 (10%)

m/z (APCI-) 438 ([M-H]⁻, 100%), 247 (10%),

10 NMR δ_{H} (DMSO-d₆) 1.18-1.26 (2H, dd, J 8.8, 11.7 Hz), 1.48 (1H, m), 1.56 (2H, d, J 12.9 Hz), 2.09 (2H, t, J 11.2 Hz), 2.90 (2H, d, J 11.2 Hz), 3.28 (2H, d, J 9.5 Hz), 3.75 (2H, s), 7.06-7.18 (4H, m), 7.20 (2H, t, J 8.5 Hz), 7.52 (1H, dd, J 2.0, 8.3 Hz), 7.91 (1H, s), 7.92 (1H, s), 12.0 (1H, br, NH)

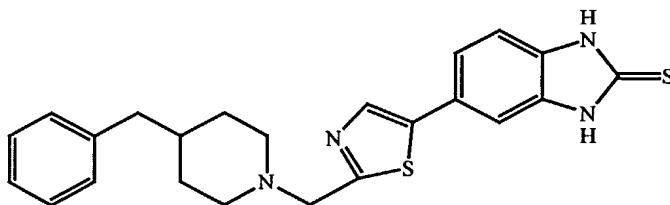
HPLC R_t = 5.49 Min; 98.023%, (20% to 100% in 12 minutes, held at 100% ACN

15 for 1 minute at 1.5 mL/min, 40 degrees. Prodigy ODS (3), 3 micron, 150 × 4.6 mm, 250 nm).

EXAMPLE 8

5-[2-(4-Benzylpiperidin-1-ylmethyl)thiazol-5-yl]-1,3-dihydrobenzimidazole-2-thione

20



25

Step 1: To a stirring solution of 4-benzylpiperidine (6) (2.00 g, 11.41 mmol) in dichloromethane (20 mL) at 0°C was added triethylamine (1.59 mL, 11.41 mmol), followed by benzyl-2-bromoacetate (1.81 mL, 11.41 mmol). After 10 minutes a white precipitate was observed. The reaction mixture was allowed to warm to room temperature. After 45 minutes the reaction mixture was condensed to dryness *in vacuo*, redissolved in EtOAc (50 mL), the organic phase washed with saturated aqueous sodium hydrogen carbonate (50 mL), and saturated brine

(50 mL). The organic phase was dried (MgSO_4) and condensed to dryness to give (4-benzylpiperidin-1-yl)acetic acid benzyl ester (3.69 g, 100%). as a pale yellow oil:

m/z (APCI+) 324 (MH^+ , 100%),

- 5 δ_{H} 1.36 (2H, dt, J 3.2, 8.8 Hz), 1.42 (1H, M) 1.60 (2H, d, J 13.2), 2.10 (2H, dt, J 2, 9.6 Hz), 2.52 (2H, d, J 6.8 Hz), 2.88 (2H, d, J 11.6 Hz), 3.21 (2H, s, N- CH_2 -CO), 5.14 (2H, s, OCH_2Ph), 7.17 (2H, d, J 7.2 Hz), 7.24 (2H, d, J 6.0 Hz).

HPLC R_t = 1.64 min; 68.1%; (5-100% MeCN in H_2O (both +0.1% trifluoroacetic acid) over 2.5 minutes at 3 mL/min, held at 100% MeCN for 0.5 minute; Prodigy

- 10 ODS III 5 μ , 50 \times 4.6 mm).

Step 2: Hydrogenolysis of (4-benzylpiperidin-1-yl)acetic acid benzyl ester, following the procedure described on Example 6, Step 2, gave (4-benzylpiperidin-1-yl)acetic acid (2.66 g, 100%) as a white solid:

ν_{max} (KBr) 1626 (C=O), 1403 cm^{-1}

- 15 m/z (APCI+) 234 (MH^+ , 100%),
 δ_{H} 1.75-1.85 (5H, m), 2.60 (2H, d, J 5.6 Hz), 2.73 (2H, m), 3.57 (2H, d, J 5.6 Hz), 3.67 (2H, d, J 11.6 Hz), 4.0 (1H, s, OH), 7.12 (2H, d, J 7.2 Hz), 7.20 (1H, d, J 7.2 Hz), 7.26 (2H, t, J 7.2 Hz).

(high performance liquid chromatography) HPLC R_t = 1.25 min; 100%; (5-100%

- 20 MeCN in H_2O (both +0.1% trifluoroacetic acid) over 2.5 minutes at 3 mL/min, held at 100% MeCN for 0.5 minute; Prodigy ODS III 5 μ , 50 \times 4.6 mm).

Step 3: To a stirred solution of 1,2-phenylenediamine (10.00 g, 0.092 mol) in dimethylformamide (150 cm^3) was added 1,1'-carbonyldiimidazole (CDI, 14.99 g, 0.092 mol). After 22 hours, the reaction mixture was evaporated and then
25 slurried in ethyl acetate. The resulting mixture was filtered, washed with ethyl acetate, and the residue dried *in vacuo* to give 1,3-dihydrobenzoimidazol-2-one (12.10 g, 98%) as a white solid:

ν_{max} (KBr) 1755 (C=O) cm^{-1}

δ_{H} (DMSO-d_6) 6.91 (4H, s, arom.), 10.55 (2H, brs, 2 \times NH).

Step 4: To a stirred slurry of aluminum trichloride (22.76 g, 170.73 mmol) in 1,2-dichloroethane (20 mL) at 0°C was added chloroacetyl chloride (15.42 g, 136.57 mmol). After 30 minutes, the substrate (9.16 g, 68.29 mmol) was added in three portions, along with further 1,2-dichloroethane (20 mL). A red-brown color was observed. The reaction mixture was heated at 50°C for 2 hours. The mixture was then poured onto ice, and the resulting mixture filtered. The residue was washed with ethanol, which gave a white solid (17.00 g). The material was recrystallized by dissolving the crude product in DMF (70 mL), heating to 80°C, adding ethanol (70 mL), cooling to ambient temperature, and then cooling further to 0°C. The resulting precipitate was collected by filtration, washed with ethanol, and dried *in vacuo* to give 5-(2-chloroethanoyl)-1,3-dihydrobenzimidazol-2-one (8.09 g, 56%) as a light brown solid:

ν_{\max} (KBr) 1747 (C=O), 1687s, 1636s, 1473s, 1398s, 1321s, 1267s, 1202s, 1157s and 1011s cm^{-1}

δ_{H} (DMSO- d_6) 5.12 (2H, s, CH_2Cl), 7.04 (1H, d, arom., J 8 Hz), 7.49 (1H, s, arom.), 7.68 (1H, dd, arom., J 8.5, 1.5 Hz), 10.96 (1H, s, arom.) and 11.11 (1H, s, arom.).

Step 5: Treatment of give 5-(2-chloroethanoyl)-1,3-dihydrobenzimidazol-2-one with sodium azide, following the procedure described in Example 6. Step 4, gave 6-(2-azidoethanoyl)-1,3-dihydrobenzimidazol-2-one (5.75 g, 93%):

ν_{\max} 3415, 2106, 1723, 1681, 1476, 1268 cm^{-1}

δ_{H} (DMSO) 4.84 (2H, s, CH_2), 7.04 (1H, d, arom., J 8.3Hz), 7.45 (1H, d, arom., J 1.2 Hz), 7.63 (1H, dd, arom., J 1.5, 8.1 Hz), 10.90-11.15 (2H, m, $\text{NH}\times 2$).

Step 6: 6-(2-Azidoethanoyl)-1,3-dihydrobenzimidazol-2-one (1.0 g, 4.6 mmol) and Pd-C (5%, 0.3g) in methanol (150mL) and concentrated HCl (2mL), were subjected to hydrogenation at 25 psi and 27°C for 1 hour. The catalyst was removed by filtration through a 'filter aid' and the solvent removed to give 6-(2-aminoethanoyl)-1,3-dihydrobenzimidazol-2-one hydrochloride (1.01 g, 96%) as a brown solid:

m/z 192.10 (MH^+)

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 ν_{\max} 3183, 1681, 1625, 1475, 1276, 1178 cm^{-1} δ_{H} (DMSO) 4.54 (2H, d, CH_2 , J 5.4 Hz), 7.08 (1H, d, arom., J 8.1 Hz), 7.52 (1H, s, arom.), 7.71 (1H, dd, arom., J 1.5, 8.1 Hz), 8.34 (3H, s, NH_3^+), 11.08 (1H, s, NH), 11.24 (1H, s, NH).

- 5 **Step 7:** Condensation of 6-(2-aminoethanoyl)-1,3-dihydrobenzimidazol-2-one hydrochloride with (4-benzylpiperidin-1-yl)acetic acid, following the procedure described in Example 6, Step 6, gave 5-[2-(4-benzylpiperidin-1-ylmethyl)thiazol-5-yl]-1,3-dihydrobenzimidazole-2-one:

 ν_{\max} (KBr) 3431br, 1730s (ketone $\text{C}=\text{O}$), 1691s, 1681s, 1645s, 1528s, 1365s,

- 10 1288s, 1232s, 815s and 750s cm^{-1}

 $\text{NMR } \delta_{\text{H}}$ (DMSO- d_6) 1.28–1.34 (2H, m), 1.49–1.57 (3H, m), 2.00 (2H, m), 2.87–2.94 (4H, m), 4.61 (2H, d, J 5.5 Hz), 7.04 (1H, d, J 8.5 Hz), 7.16–7.20 (3H, m), 7.27–7.30 (2H, m), 7.48 (1H, s), 7.69 (1H, dd, J 8.5 and 1.5 Hz), 7.98 (brs, 1H, amide NH), 10.94 and 11.11 (each 1H, s, $2 \times \text{NH}$):

- 15 m/z (APCI+) 407 (MH^+ , 60%) and 169 (100%),

HPLC R_t = 3.74 min; 96.11%; (20–100% MeCN in H_2O (both +0.1%trifluoroacetic acid) over 12 minutes at 1.5 mL/minute, held at 100% MeCN for 1 minute; Prodigy ODS III 3 μ , 150 \times 4.6 mm, 40°C).**Step 8:** Treatment of 5-[2-(4-benzylpiperidin-1-ylmethyl)thiazol-5-yl]-1,3-

- 20 dihydrobenzimidazole-2-thione with Lawesson's reagent, following the procedure described in Example 6, Step 7, gave 5-[2-(4-benzylpiperidin-1-ylmethyl)thiazol-5-yl]-1,3-dihydrobenzimidazole-2-thione.

Purified by preparative HPLC (10–100% ACN (0.1% TFA) over 30 minutes, held at 100% for 5 minutes at 20 mL/minute, YMC-PACK ODS-A, 5 micron, 100 \times

- 25 30 mm, 254 nm). Yellow solid (0.031 g, 6%).

 ν_{\max} (KBr) 3420br, 3124br, 2921ms, 1613w, 1511w, 1466s (C(S)NH), 1333ms (NC(S)N), 1190s, 807ws, m/z (APCI+) 421 (MH^+ , 100%), 248 (10%) m/z (APCI-) 419 ($[\text{M}-\text{H}]^-$, 100%), 246 (10%),

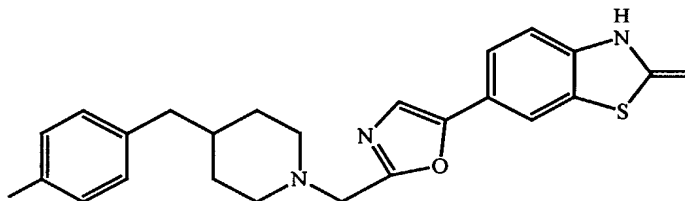
72

NMR δ_{H} (DMSO- d_6) 1.23 (2H, m), 1.51 (1H, m), 1.54 (2H, d, J 12.2 Hz), 2.04 (2H, t, J 11.0 Hz), 2.88 (2H, d, J 11.2 Hz), 3.26 (2H, d, J 10.0 Hz), 3.75 (2H, s) 7.15 (4H, d, arom., J 8.0 Hz), 7.25 (3H, t, arom., J 8.3 Hz), 7.40 (1H, d, arom., J 8.3 Hz), 8.0 (1H, s, arom.)

- 5 HPLC R_t = 5.94 minutes, 97.48%, (20-100% ACN (0.1% TFA) in 20 minutes, held at 100% ACN for 1 minute at 1.5 mL/minute, 40°C. liquid chromatography-mass spectrometry (LC-MS) Prodigy ODS(3), 3 micron, 150 \times 4.6 mm 250 nm.

EXAMPLE 9

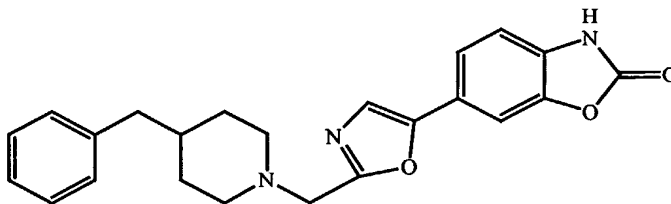
- 6-{2-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]oxazol-5-yl}-3*H*-benzothiazol-2-one
10 one



- ν_{max} (KBr) 3436br, 1682 (amide C=O), 1508s, 1468s, 1346s, 1270s, 1175s, 1136s, 1087s, 989s, 947s, 822s, and 783s cm^{-1}
NMR δ_{H} (DMSO- d_6) 1.40-1.50 (2H, m), 1.75-1.79 (3H, m), 3.05-3.10 (2H, m),
15 3.55-3.58 (2H, m), 4.59 (2H, brs), 7.12 (2H, t, J 9 Hz), 7.21 (2H, t, J 8 Hz), 7.67 (1H, dd, J 9 and 1.5 Hz), 7.75 (1H, s), 7.86 (1H, s), 8.00 (1H, d, J 8 Hz) and 9.95 (1H, brs),
 m/z (APCI-) 422 ($[\text{M}-\text{H}]^-$ 100%),
HPLC R_t = 4.55 min; 96.86%; (20-100% MeCN in H_2O (both +0.1%
20 trifluoroacetic acid) over 7 minutes at 1.5 mL/minute, held at 100% MeCN for 1 minute; Prodigy ODS III 5 μ , 250 \times 4.6 mm, 40°C).

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EXAMPLE 10

6-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-3*H*-benzoxazol-2-one**Step 1:** Coupling of (4-benzylpiperidin-1-yl)acetic acid with **39**, following the

5 procedure described in Example 6, Step 6, gave 2-(4-benzylpiperidin-1-yl)-*N*-[2-oxo-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]acetamide:

ν_{\max} (KBr) 3380w, 3091w, 3023m, 2911w, 1773s, 1676w, 1648s, 1616m,

1528m, 1450m, 1424m, 1353w, 1266s, 923m, 912m, and 748m cm^{-1}

NMR δ_{H} (DMSO- d_6) 1.17-1.33 (2H, m), 1.50-1.57 (3H, m), 1.99-2.04 (2H, m),

10 2.87-2.89 (2H, m), 2.94 (2H, s), 3.29 (2H, s), 4.61 (2H, d, J 5.5 Hz), 7.16-7.21 (4H, m), 7.28 (2H, t, J 8 Hz), 7.84-7.87 (2H, m), and 8.01 (1H, brs, amide NH):

m/z (APCI+) 408 (MH^+ , 100%),

m/z (APCI-) 406 ($[\text{M}-\text{H}]^-$, 100%),

HPLC R_t = 5.30 min; 96.05%; (20-100% MeCN in H_2O (both +0.1%

15 trifluoroacetic acid) over 20 minutes at 1.5 mL/minute, held at 100% MeCN for 3 minutes; Prodigy ODS III 3 μ , 150 \times 4.6 mm, 40°C).

Step 2: 6-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-3*H*-benzoxazol-2-one was prepared from 2-(4-benzylpiperidin-1-yl)-*N*-[2-oxo-2-(2-oxo-2,3-dihydrobenzoxazol-6-yl)ethyl]acetamide following the procedure described in

20 Example 9, Step 1:

ν_{\max} (KBr) 3435br, 1783s, 1766s, 1495m, 1485m, 1311m, 1286m, 128m,

1053m, 968w, and 753w cm^{-1}

NMR δ_{H} (DMSO- d_6) 1.20-1.40 (2H, m), 1.25-1.70 (3H, m), 2.10-2.40 (2H, m),

2.90-3.10 (2H, m), 3.70-3.85 (2H, m), 7.16-7.26 (4H, m), 7.48-7.63 (3H, m) and

25 11.82 (1H, brs)

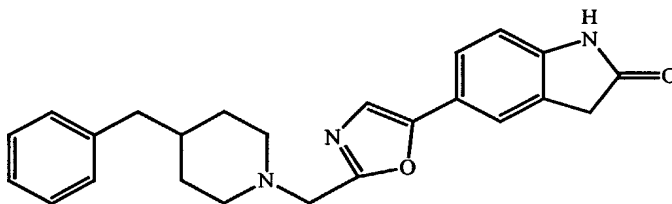
m/z (APCI+) 390 (MH^+ , 18%) and 169 (100)

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HPLC R_t = 6.26 min; 95.61%; (20-100% MeCN in H_2O (both +0.1% trifluoroacetic acid) over 20 minutes at 1.5 mL/minute, held at 100% MeCN for 3 minutes; Prodigy ODS III 3 μ , 150 \times 4.6 mm, 40°C).

EXAMPLE 11

5 5-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-1,3-dihydroindol-2-one



Step 1: 5-(2-Chloroethanoyl)-1,3-dihydroindol-2-one was prepared following the procedure described in Example 6, Step 3:

δ_H (d_6 -Me₂SO) 3.57 (2H, s, ArCH₂C(O)NH), 5.08 (2H, s, CH₂Cl), 6.93 (1H, d, 10 arom., J 8.0 Hz), 7.83 (1H, s, arom.), 7.88 (1H, d, arom., J 8.0 Hz) and 10.82 (1H, brs, NH),

m/z (APCI-) 210 and 208 (each [M-H]⁻, 35 and 100%).

Step 2: Treatment of 5-(2-chloroethanoyl)-1,3-dihydroindol-2-one with sodium azide, following the procedure described in Example 6, Step 4, gave 6-(2-

15 azidoethanoyl)-1,3-dihydroindol-2-one (6.58 g, 91%):

m/z 215.08 (M-H⁻)

ν_{max} 3229, 2122, 1715, 1679, 1615, 1236, 1123, 824 cm⁻¹

δ_H (DMSO) 3.57 (2H, s, CH₂CO), 4.79 (2H, s, CH₂N₃), 6.93 (1H, d, arom., 20 J 8.1 Hz), 7.79 (1H, s, arom.), 7.83 (1H, s, arom., J 8.3 Hz), 10.78 (1H, bs, NH).

Step 3: Reduction of 6-(2-azidoethanoyl)-1,3-dihydro-indol-2-one, following the procedure described in Example 6, Step 5, gave 6-(2-aminoethanoyl)-1,3-dihydroindol-2-one hydrochloride (2.96 g, 63%):

m/z 191.05 (MH⁺)

ν_{max} 3401, 3205, 1687, 1619, 1493, 1423, 1312, 1247 cm⁻¹

75

δ_{H} (DMSO) 3.58 (2H, s, CH_2CO), 4.49 (2H, d, CH_2 , J 5.4 Hz), 6.98 (1H, d, arom., J 8.3 Hz), 7.87 (1H, s, arom.), 7.92 (1H, d, arom., J 8.3 Hz), 8.35 (3H, s, NH_3^+), 10.95 (1H, s, NH).

Step 4: Condensation of 6-(2-aminoethanoyl)-1,3-dihydroindol-2-one

- 5 hydrochloride with (4-benzylpiperidin-1-yl)acetic acid, following the procedure described in Example 6, Step 6, gave 2-(4-benzyl-piperidin-1-yl)-*N*-[2-oxo-2-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)ethyl]acetamide:

ν_{max} (KBr) 3352br, 3173br, 2918m, 1717s (ketone $\text{C}=\text{O}$), 1679s, 1649s, 1621s, 1523s, 1361s, 1252s, 1101s

- 10 m/z (APCI+) 406 (MH^+ , 100%), 169 (25%)

m/z (APCI-) 404 ($[\text{M}-\text{H}]^-$, 100%).

NMR δ_{H} (DMSO- d_6) 1.31 (2H, dt, J 3.0, 12.4 Hz), 1.51 (1H, m), 1.54-1.57 (2H, d, J 12.4 Hz), 2.86 (2H, d, J 11.6 Hz), 2.92 (2H, s), 3.29 (2H, d, J 9.2 Hz), 3.56 (2H, s), 4.56 (2H, d, J 6 Hz), 6.90 (1H, d, J 8 Hz), 7.18 (3H, m), 7.26 (2H, t, arom., J 7.2 Hz) 7.90 (1H, d, arom., J 8.4 Hz) 7.95 (1H, t, arom., J 5.6)

- 15 HPLC R_t = 4.00 Min; 97.49%, (20-100% ACN (0.1% TFA) in 12 minutes, held at 100% acetonitrile (ACN) for 1 minute at 1.5 mL/minute, 40 degrees. Prodigy ODS (3), 3 micron, 150 \times 4.6 mm, 250 nm.

Step 5: 5-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-1,3-dihydroindol-2-one

- 20 prepared from 2-(4-benzyl-piperidin-1-yl)-*N*-[2-oxo-2-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)ethyl]acetamide following the procedure described in Example 9, Step 1:

ν_{max} (KBr) 3439br, 1697s, 1624m, 1485m, 1239m, 1112m, 1050m and 815m cm^{-1}

- 25 NMR δ_{H} (DMSO- d_6) 1.15-1.18 (2H, m), 1.20-1.46 (3H, m), 2.02 (2H, t, J 11 Hz), 2.83 (2H, d, J 12 Hz), 3.54 (2H, s), 3.63 (2H, s), 6.89 (1H, d, J 8 Hz), 7.13-7.18 (3H, m), 7.24-7.28 (2H, m), 7.42 (1H, s), 7.49 (1H, d, J 8 Hz), 7.53 (1H, s) and 10.53 (1H, s, amide NH)

m/z (APCI+) 388 (MH^+ , 100%)

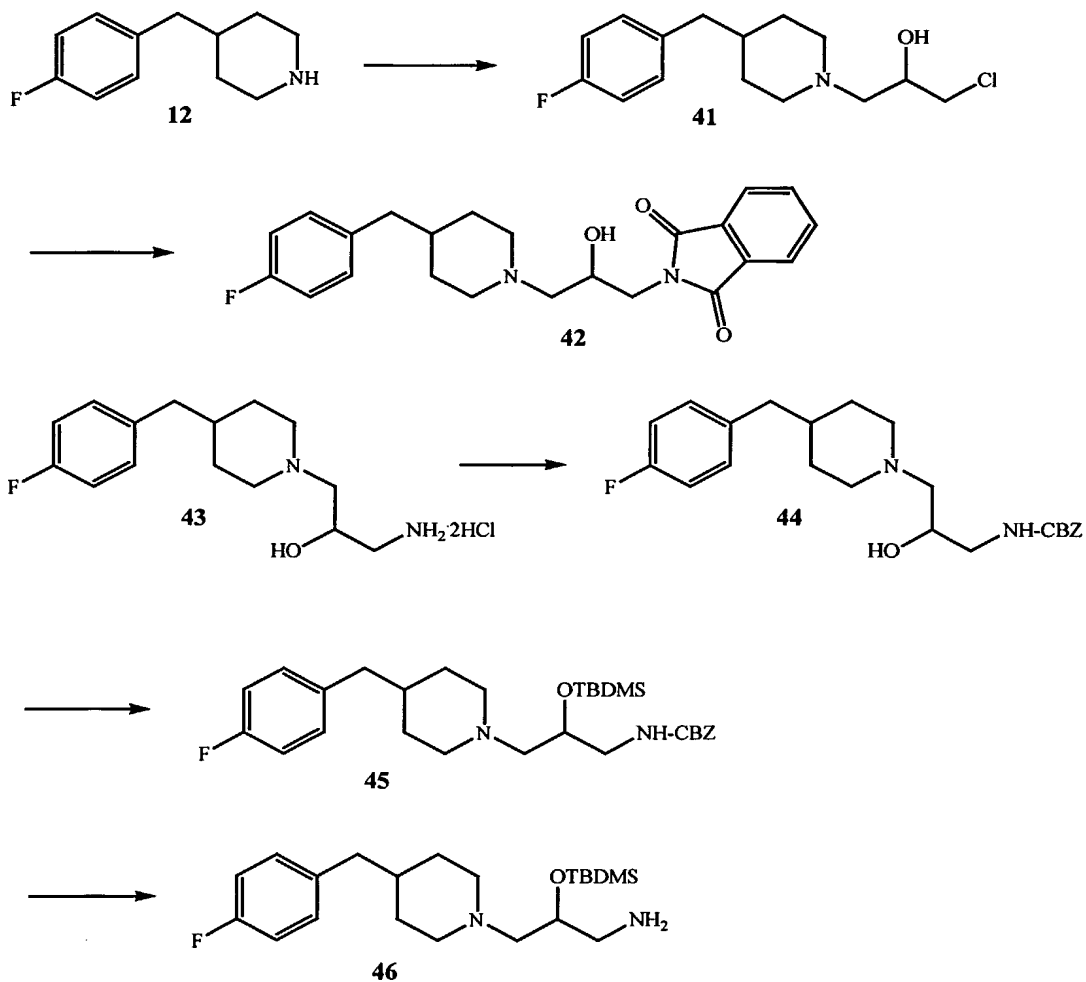
- 30 m/z (APCI-) 386 ($[\text{M}-\text{H}]^-$, 100%)

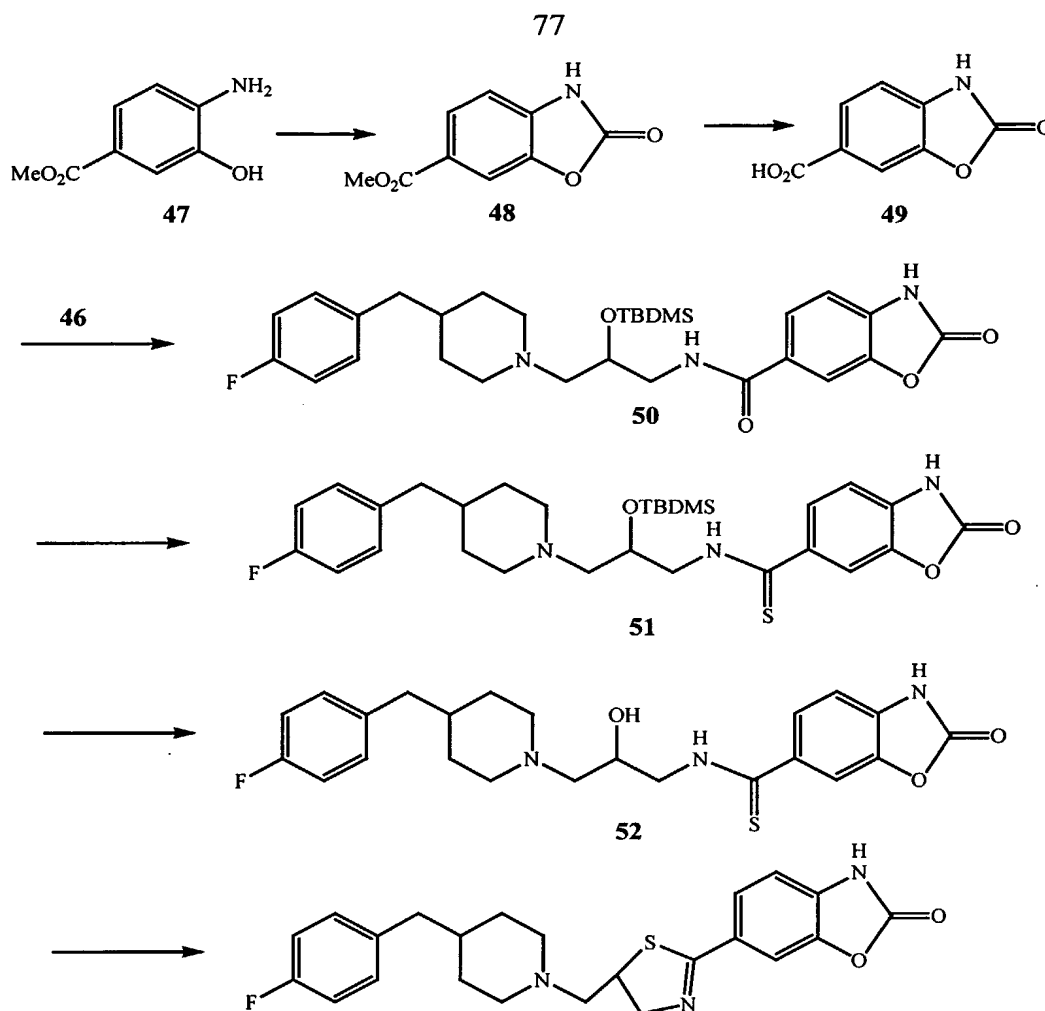
76

HPLC R_t = 4.40 minutes; 99.40%; (20–100% MeCN in H₂O (both +0.1% trifluoroacetic acid) over 12 minutes at 1.5 mL/minute, held at 100% MeCN for 1 minute; Prodigy ODS III 3 μ , 150 \times 4.6 mm, 40°C).

EXAMPLE 12

- 5 6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydrothiazol-2-yl}-3*H*-benzoxazol-2-one





Step 1: 4-(4-Fluorobenzyl)piperidine hydrochloride (**12**) (20.0 g, 87.1 mmol), epichlorohydrin (8.06 g, 87.0 mmol) and triethylamine (8.80 g, 87.1 mmol) in EtOH (200 mL) were stirred at ambient temperature for 96 hours. The solvent was removed and the material taken up in EtOAc, washed with saturated NaHCO₃, brine and dried (MgSO₄) to give **41** (16.69 g, 67%) as an orange solid:

¹H-NMR (CDCl₃) δ_{H} *inter alia* 1.22-1.35 (2H, m), 1.47-1.53 (1H, m), 1.62 (2H, dd, *J* 13 and 2.5 Hz), 1.95 and 2.24 (each 1 H, dt, *J* 11.5, 2.5 and 2.5 Hz), 2.42-2.44 (2H, m, CH₂Ph), 2.50 (2H, d, *J* 7 Hz), 2.80 and 2.94 (each 1 H, d, *J* 11.5 Hz), 3.55 (2H, d, *J* 5 Hz, CH₂Cl), 3.87-3.93 (1H, m, CHOH), 6.93-6.99 and 7.06-7.10 (each 2H, m)

m/z (APCI⁺) 286 (MH⁺, 100%) and 250 ([M-Cl]⁺, 60).

Step 2: Compound 41 (16.69 g, 58.46 mmol) and potassium phthalimide (10.81 g, 58.46 mmol) in DMF (100 mL) were heated to 100°C for 2 hours. The solvent was removed and the material taken up in EtOAc, washed with brine dried (MgSO₄) and evaporated. The residue was partially purified by silica gel column chromatography (CH₂Cl₂) to yield a 1:1 mixture of **42** and phthalimide (13.91 g, 44%) as a white solid:

¹H-NMR (CDCl₃) δ_H 1.16-1.30 (2H, m), 1.43-1.51 (3H, m), 1.88 and 2.20 (each 1 H, dt, *J* 11.5 and 2.5 Hz), 2.33-2.43 (2H, m), 2.47 (2H, d, *J* 7 Hz), 2.78 and 2.89 (each 1H, d, *J* 4.5 Hz), 3.63-3.82 (2H, m), 3.94-4.02 (1H, m), 6.97 (2H, t, *J* 11 Hz), 7.05-7.08 (2H, m), 7.69-7.79 (2H, m) and 7.84-7.89 (2H, m) *m/z* (APCI+) 267 (MH⁺, 100%).

Step 3: Compound **42** (13.91 g, 25.6 mmol – impure mixture) and hydrazine hydrate (3.84 g, 76.89 mmol) in ethanol (100 mL) and water (100 mL) were heated under reflux conditions for 3 hours, and then left to stir at ambient temperature for 16 hours. The solvent was removed, and the crude material was acidified with 10% aqueous hydrochloric acid. The precipitate was filtered and the pad washed with water; the filtrate was concentrated to yield **43** (13.5 g, >100%, wet) as a yellow solid which was partially dried *in vacuo*:

NMR δ_H (MeOH-d₄) *inter alia* 1.55-1.69 (2H, m), 1.85-1.92 (3H, m), 2.60 (2H, d, *J* 6.5 Hz), 2.86-3.24 (6H, m), 3.60-3.68 (2H, m), 4.30-4.36 (1H, m), 7.01 (2H, t, *J* 8.5 Hz) and 7.18-7.24 (2H, m) *m/z* (APCI+) 267 (MH⁺, 100%).

Step 4: Benzyl chloroformate (4.26 g, 25.0 mmol) was added to a mixture of **43** (5.92 g, 17.57 mmol) and sodium carbonate decahydrate (21.45 g, 75.0 mmol) in dioxane-water (100-10 mL), and the resulting mixture stirred at ambient temperature for 4 hours. The solvent was removed, the material diluted with EtOAc, washed with water followed by brine, and then dried (MgSO₄) and evaporated. The product was purified by column chromatography (silica gel, 0% to 5% MeOH in CH₂Cl₂) **44** (2.10 g, 30%) as a clear oil which solidified on standing:

m/z 401.21 (MH^+)

ν_{\max} 3339, 2924, 1716, 1509, 1220 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ_{H} 1.25 (3H, m, alkyl), 1.60 (2H, m, alkyl), 1.82 (1H, m, alkyl), 2.22 (1H, m, alkyl), 2.28 (2H, d, CH_2 , J 7.2 Hz), 2.49 (2H, d, CH_2 ,

5 J 7.2 Hz), 2.72 (1H, d, CHH , J 12.0 Hz), 2.93 (1H, d, CHH , J 12.0 Hz), 3.10 (1H, m, CHH), 3.41 (1H, m, CHH), 3.70 (1H, m, CHO), 5.10 (2H, s, CH_2O), 5.20 (1H, bs, NH), 6.98 (2H, m, arom.), 7.07 (2H, m, arom.), 7.32 (5H, m, Ph).

Step 5: *tert*-Butyldimethylsilyl trifluorosulfonate (1.94 g, 7.35 mmol) was added to a cooled (0°C) solution of **44** (2.10 g, 5.25 mmol) and 2,6-lutidine (1.12 g,

10 10.50 mmol) in dichloromethane (20 mL). After 15 minutes, the mixture was diluted with dichloromethane, washed with saturated NaHCO_3 followed by brine, and then dried (MgSO_4) and evaporated to give **45** (2.80 g, quantitative) as a clear oil:

m/z 515.29 (MH^+)

15 ν_{\max} 3350, 1721, 1510, 1255, 1222 cm^{-1} .

Step 6: Compound **45** (2.70 g, 5.25 mmol) was hydrogenated at 50 psi and 30°C in the presence of $\text{Pd}(\text{OH})_2\text{-C}$ (100 mg) in MeOH (20 mL) for 8 hours. The mixture was filtered through a 'filter-aid' and the solvent removed to yield **46** (1.83 g, 92%) as a clear gum:

20 m/z 381.31 (MH^+)

ν_{\max} 3382, 2928, 1510, 1030, 837 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ_{H} 0.08 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.88 (9H, s, ^tBu), 1.25 (2H, m, CH_2), 1.45 (1H, m, CH), 1.60 (2H, m, CH_2), 2.02 (2H, m, CH_2), 2.25 (2H, bs, NH_2), 2.47 (4H, m, 2x CH_2), 2.88 (2H, d, CH_2 , J 4.4 Hz), 2.89 (2H, bt, CH_2 ,

25 J 12.0 Hz), 3.81 (1H, m, CHO).

Step 7: Methyl 4-amino-3-hydroxybenzoate (**47**) (11.01 g, 65.9 mmol) and CDI (11.21 g, 69.2 mmol) were stirred in DMF (75 mL) at room temperature for 1 hour. The DMF was then removed and the mixture diluted with EtOAc, washed

with 0.5 M NaOH, 10% HCl, brine and dried (MgSO₄) to give **48** (7.52 g, 59%) as a brown solid:

m/z 191.98 (M-H)⁻

ν_{\max} 3402, 1746, 1708, 1290 cm⁻¹

- 5 ¹H-NMR (CDCl₃) δ_H (DMSO-d₆) 3.85 (3H, s, OCH₃), 7.19 (1H, d, arom., J 8.4 Hz), 7.76 (1H, d, arom., J 1.6 Hz), 7.82 (1H, dd, arom., J 1.6, 8.4 Hz), 12.07 (1H, bs, NH).

Step 8: Compound **48** (8.0 g, 41.5 mmol) and LiOH·H₂O (3.49 g, 83.0 mmol) in MeOH-H₂O (100-10 mL) were heated under reflux conditions for 4 hours. An

- 10 aliquot of LiOH·H₂O (1.75 g, 42.0 mmol) was added and the heating continued for a further 3 hours. The solvent was removed, and the solids were slurried in 10% HCl then filtered and washed with H₂O and dried *in vacuo* to give **49** (7.40 g, quantitative) as a brown solid:

m/z 177 (M-H)⁻

- 15 ν_{\max} 3431, 3120, 1769, 1685, 1619, 1427, 1296 cm⁻¹

NMR δ_H (DMSO-d₆) 7.17 (1H, d, arom., J 8.4 Hz), 7.40 (1H, d, arom., J 1.2 Hz), 7.80 (1H, dd, arom., J 1.2, 8.4 Hz), 12.02 (1H, bs, NH), 13.89 (1H, bs, OH).

Step 9: Compound **49**

(980 mg, 69%) as a brown foam:

- 20 m/z 542.27 (MH⁺)

¹H-NMR (CDCl₃) δ_H 0.12 (3H, s, SiCH₃), 0.13 (3H, s, SiCH₃), 0.89 (9H, s, Si^tBu), 1.66 (1H, bs, alkyl), 1.80 (2H, bs, alkyl), 2.40 (2H, bs, alkyl), 2.57 (2H, m alkyl), 2.79 (1H, bs, alkyl), 2.96 (1H, bs, alkyl), 3.31 (1H, bs, alkyl), 3.53 (2H, bs, alkyl), 3.66 (2H, m, alkyl), 4.20 (1H, bs, CHO), 6.96-7.12 (5H, m, arom.), 7.58 (1H, s, arom.), 7.66 (1H, d, arom., J 8.0 Hz), 7.99 (1H, bs, NH).

- 25 **Step 10:** Compound **50** (980 mg, 1.81 mmol) and Lawesson's reagent (366 mg, 906 μ mol) in dioxane (5 mL) were heated under reflux conditions for 1 hour. A further aliquot of Lawesson's reagent (732 mg, 1.81 mmol) was added, and heating continued for 1.5 hours. The solvent was removed and the product was

diluted with EtOAc, washed extensively with saturated NaHCO₃, brine, and dried. The product was purified by chromatography (silica gel, 0-50% EtOAc in heptane) to give 6-[5-(4-(4-fluorobenzyl)piperidin-1-ylmethyl)-4,5-dihydro-thiazol-2-yl]-3*H*-benzoxazol-2-one (194 mg, 25%) as a white solid:

5 m/z 426.18 (MH⁺)

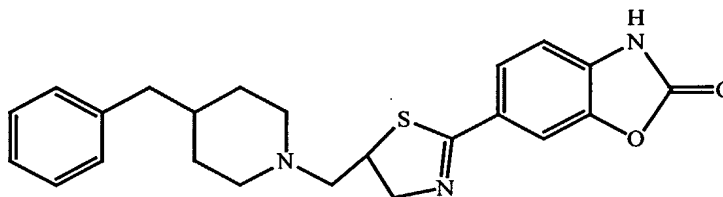
ν_{\max} 1773, 1509 cm⁻¹

¹H-NMR (CDCl₃) δ_{H} 1.25 (2H, m, alkyl), 1.56 (3H, m, alkyl), 1.97 (2H, t, CH₂, *J* 11.2 Hz), 2.56 (4H, m, alkyl), 2.89 (2H, bm, alkyl), 4.11 (1H, 1, CHS, *J* 6.4 Hz), 4.35 (2H, m, CH₂N), 6.96 (2H, m, arom.), 7.06 (3H, m, arom.), 7.63 (1H, dd, arom., *J* 1.0, 8.0 Hz), 7.73 (1H, d, arom., *J* 1.2 Hz)

HPLC Rt = 3.81 minutes, 99.10% (20-100% MeCN in H₂O (both +0.1% formic acid) over 7 minutes at 1.5 mL/min; Prodigy ODS III 3 μ , 150 \times 4.6 mm, 40°C)

EXAMPLE 13

6-[5-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzoxazol-2-one



Step 1: Treatment of amine 6 with epichlorohydrin, following the procedure described in Example 12, Step 1, gave crude 1-chloro-3-(4-benzylpiperidin-1-yl)propan-2-ol (29.03 g, >100%) as a clear, colorless oil:

20 ν_{\max} (neat) 3300 (brs, OH), 2921s, 1603m, 1494m, 1453s, 1091s, 1058s, 747s

¹H-NMR (CDCl₃) δ_{H} 1.24-1.30 (2H, m), 1.50-1.60 (1H, m), 1.61-1.65 (2H, m), 1.93, 2.24 (each 1 H, dt, *J* 11.5 and 2 Hz), 2.36-2.46 (2H, m), 2.53 (2H, d, *J* 7 Hz, CH₂N), 2.78, 2.92 (each 1H, d, *J* 12 Hz, CH₂Ph), 3.53-3.55 (2H, m, CH₂Cl), 3.86-3.92 (1H, m, CHOH), 7.09-7.29 (5H, m, Ph)

25 m/z (APCI⁺) 270 and 268 (each MH⁺, 40 and 100%) and 232 ([M-Cl]⁺, 40).

Step 2: Treatment of 1-chloro-3-(4-benzylpiperidin-1-yl)propan-2-ol with potassium phthalimide, following the procedure described in Example 12, Step 2, gave 2-[3-(4-benzylpiperidin-1-yl)-2-hydroxypropyl]isoindole-1,3-dione (32.44 g, 86%) as a white solid:

- 5 $^1\text{H-NMR}$ (CDCl_3) δ_{H} 1.13-1.35 (2H, m), 1.45-1.49 (1H, m), 1.50-1.58 (2H, m), 1.87 and 2.19 (each 1H, dt, J 11.5, 11.5 and 2 Hz), 2.31-2.45 (2H, m), 2.50 (2H, d, J 7 Hz, $\text{NCH}_2\text{CH}(\text{OH})$), 2.76 and 2.86 (each 1H, d, J 12 Hz), 3.68 and 3.79 (each 1H, dd, J 13.5 and 4.5 Hz, CH_2N), 3.96-4.03 (1H, m, CHOH), 7.10-7.28 (5H, m, Ph), 7.68-7.75, and 7.82-7.86 (each 2H, m, phthalimide)
- 10 m/z (APCI+) 379 (MH^+ , 100%).

Step 3: Treatment of 2-[3-(4-benzylpiperidin-1-yl)-2-hydroxypropyl]-isoindole-1,3-dione with hydrazine hydrate, following the procedure described in Example 12, Step 3, gave 1-amino-3-[4-benzylpiperidin-1-yl]propan-2-ol *bis*-hydrochloride salt (24.32 g) as a yellow hygroscopic solid:

- 15 ν_{max} (KBr) 3418br, 2934br, 1712m, 1603m, 1494m, 1454m, 1066m, 945m and 748m
- NMR δ_{H} (CD_3OD) 1.59-1.62 (2H, m), 1.86-1.93 (3H, m), 2.61 (2H, d, J 6.5 Hz), 2.90-3.31 (6H, m), 3.60-3.64 (2H, m), 4.30-4.40 (1H, m, CHOH), 7.17-7.20 (2H, m) and 7.22-7.26 (2H, m).
- 20 m/z (APCI+) 249 (MH^+ , 100%).

- Step 4:** To a stirring solution of 1-amino-3-(4-benzylpiperidin-1-yl)propan-2-ol (2.00 g, 6.23 mmol) in 1,4-dioxan/ H_2O (4:1, 25 mL) was added solid sodium hydroxide (0.28 g, 6.85 mmol). On full dissolution of the sodium hydroxide, dibenzyl dicarbonate (1.96 g, 6.85 mmol) was added. The resulting solution was
- 25 stirred for 22 hours. The reaction mixture was condensed to dryness *in vacuo* to give a yellow gum. This was redissolved in EtOAc, washed with saturated aqueous sodium bicarbonate solution, and saturated brine. The organic phase was dried (MgSO_4) and condensed to dryness *in vacuo* to give a yellow oil. The oil was subject to column chromatography [silica gel, MeOH-DCM (0-20% MeOH over 30

minutes)] to give [3-(4-benzylpiperidin-1-yl)-2-hydroxypropyl]carbamic acid benzyl ester (1.64 g, 69%) as an orange solid:

m/z (APCI+) 383 (MH^+ , 100%)

1H -NMR ($CDCl_3$) δ_H 1.2-1.3 (2H, m), 1.5 (1H, m), 1.60 (2H, d, J 13.1 Hz), 1.85

5 (1H, t, J 11.2 Hz), 2.20 (1H, t, J 11.2 Hz), 2.27 (2H, d, J 6.8 Hz), 2.51 (2H, d, J 7.0 Hz), 2.70 (1H, d, J 11.2 Hz), 2.90 (1H, d, J 11.2 Hz), 3.10 (1H, m), 3.40 (1H, d, J 3.6 Hz), 3.70 (1H, d, J 3.4 Hz), 5.10 (2H, s, CH_2O), 5.25 (1H, s, NH), 7.11 (2H, d, arom., J 7.2 Hz), 7.18 (1H, t, arom., J 7.6 Hz), 7.25-7.35 (7H, m, arom.)

HPLC R_t = 1.62 min; 71.1%; (5–100% MeCN in H_2O (both +0.1% trifluoroacetic

10 acid) over 2.5 minutes at 3 mL/minute, held at 100% MeCN for 0.5 minute; Prodigy ODS III 5 μ , 50 \times 4.6 mm).

Step 5: Treatment of [3-(4-benzylpiperidin-1-yl)-2-hydroxypropyl]carbamic acid benzyl ester with *tert*-Butyldimethylsilyl trifluorosulfonate, following the procedure described in Example 12, Step 5, gave {2-(*tert*-

15 butyldimethylsilyloxy)-3-[4-benzylpiperidin-1-yl]propyl}carbamic acid benzyl ester as a yellow oil:

m/z 497.42 (MH^+)

ν_{max} 3353, 2927, 1726, 1253, 1100, 836 cm^{-1}

1H -NMR ($CDCl_3$) δ_H 0.05 (6H, s, $Si(CH_3)_2$), 0.86 (9H, s, Si^tBu), 1.25 (2H, m, alkyl), 1.45 (1H, m, CH), 1.60 (2H, m, alkyl), 1.90 (2H, m, alkyl), 2.33 (2H, d, 2 \times CH, J 6.0 Hz), 2.48 (2H, d, CH_2 , J 7.2 Hz), 2.83 (2H, bd, CH_2 , J 10.4 Hz), 3.27 (2H, m, CH_2), 3.82 (1H, m, CHO), 5.10 (2H, s, CH_2O), 5.85 (1H, bm, NH), 7.11 (2H, m, arom.), 7.18 (1H, m, arom.), 7.28-7.37 (5H, m, arom.).

Step 6: Hydrogenation of {2-(*tert*-butyldimethylsilyloxy)-3-[4-benzylpiperidin-1-yl]propyl}carbamic acid benzyl ester, following the procedure described in Example 12, Step 6, gave {2-(*tert*-butyldimethylsilyloxy)-3-[4-benzylpiperidin-1-yl]-propylamine as a white semi-solid:

m/z 363.19 (MH^+)

ν_{max} 2927, 1252, 1075, 836, 770 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ_{H} 0.075 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3), 0.89 (9H, s, Si^tBu), 1.28 (1H, m, alkyl), 1.63 (5H, m, alkyl, NH_2), 1.92 (2H, m, alkyl), 2.30 (2H, d, $2 \times \text{CH}$), 2.51 (2H, d, CH_2 , J 6.8 Hz), 2.69 (1H, dd, CH, J 5.2, 12.8 Hz), 2.78 (0.5H, d, $0.5 \times \text{CH}$, J 4.4 Hz), 2.82 (2.5H, m, alkyl), 3.73 (1H, m, CHO), 7.14 (2H, m, arom.), 7.20 (1H, m, arom.), 7.26 (2H, m, arom.).

Step 7: Compound **49** (271 mg, 1.51 mmol), HBTU (574 mg, 1.51 mmol) and DIPEA (391 mg, 3.03 mmol) were stirred in DMF (5 mL) for 10 minutes, then {2-(*tert*-butyldimethylsilanyloxy)-3-[4-(benzyl)piperidin-1-yl]propylamine (548 mg, 1.51 mmol), was added and stirring continued for 1 hour. The solvent was removed, and the mixture diluted with EtOAc, washed with saturated NaHCO_3 , brine and dried (MgSO_4). The crude material was purified by chromatography (silica gel, CH_2Cl_2) to give 2-oxo-2,3-dihydrobenzoxazole-6-carboxylic acid [3-(4-benzylpiperidin-1-yl)-2-(*tert*-butyldimethyl-silanyloxy)propyl]amide (786 mg, 99%) as a brown foam:

m/z 542.22 (MH^+)

ν_{max} 3376, 2929, 1781, 1640, 1494, 840 cm^{-1} .

Step 8: 2-Oxo-2,3-dihydrobenzoxazole-6-carboxylic acid [3-(4-benzylpiperidin-1-yl)-2-(*tert*-butyldimethylsilanyloxy)propyl]amide (686 mg, 1.31 mmol) and Lawesson's reagent (530 mg, 1.31 mmol) in dioxane (5 mL) were heated under reflux conditions for 2 hours. The solvent was removed, and the product was purified by chromatography (silica gel, 0-50% EtOAc in heptane) to give 2-oxo-2,3-dihydrobenzoxazole-6-carbothioic acid [3-(4-benzylpiperidin-1-yl)-2-(*tert*-butyldimethylsilanyloxy)propyl]amide (559 mg, 79%): as a green gum:

m/z 540.33 (MH^+)

ν_{max} 3218, 1771, 1595, 1495, 1255, 1108 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) δ_{H} aliphatics of little use due to rotamers, 7.07 (1H, d, arom., J 7.2 Hz), 7.20 (1H, d, arom., 7.2 Hz), 7.21-7.29 (5H, m, Ph), 7.74 (1H, s, arom.).

Step 9: Tetrabutylammonium fluoride (TBAF) (1.24 μmol , 1.24 mL, 1 M in THF) was added to a mixture of 2-oxo-2,3-dihydrobenzoxazole-6-carbothioic acid [3-(4-

benzylpiperidin-1-yl)-2-(*tert*-butyldimethylsilyloxy)propyl]amide (336 mg, 623 μ mol) and 4Å molecular sieves (1 g) in THF (2 mL). After stirring at room temperature for 1.5 hours, the mixture was diluted with EtOAc, washed with saturated NaHCO₃, brine and dried (MgSO₄) to yield 2-oxo-2,3-

- 5 dihydrobenzoxazole-6-carbothioic acid [3-(4-benzylpiperidin-1-yl)-2-hydroxypropyl]amide (280 mg, quantitative) as a solid yellow foam:

m/z 426.29 (MH⁺)

ν_{\max} 3306, 2924, 1770, 1660, 1264, 1059 cm⁻¹

¹H-NMR (CDCl₃) δ_H some TBAF still present, hence aliphatics unclear; 2.52

- 10 (2H, d, CH₂, J 7.2 Hz), 2.80 (1H, d, CHH, J 11.2 Hz), 2.99 (1H, d, CHH, J 11.2 Hz), 3.25 (2H, m, CH₂), 3.83 (1H, m, OH), 4.07 (1H, m, CHO), 7.05 (1H, d, arom., J 8.4 Hz), 7.12 (2H, d, arom., J 8.4 Hz), 7.20 (1H, d, arom., J 7.2 Hz), 7.28 (2H, m, arom.), 7.59 (1H, d, arom., J 8.0 Hz), 7.12 (1H, d, arom., J 1.6 Hz), 8.42 (1H, bs, NH). **Step 10:** 2-Oxo-2,3-dihydrobenzoxazole-6-carbothioic acid [3-
- 15 (4-benzylpiperidin-1-yl)-2-hydroxypropyl]amide (240 mg, 565 μ mol) and Burgess reagent (134 mg, 565 μ mol) in THF (5 mL) were heated under reflux conditions for 1 hour. The mixture was diluted with EtOAc, washed with saturated NaHCO₃, brine and dried (MgSO₄). Purification by chromatography (silica gel, CH₂Cl₂) gave the product as a yellow foam (91 mg), this was then repurified by
- 20 chromatography (silica gel, 0-50% EtOAc in heptane) to give 6-[5-(4-benzylpiperidin-1-ylmethyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzoxazol-2-one (52 mg, 23%) as an off white solid:

m/z 408.21 (MH⁺)

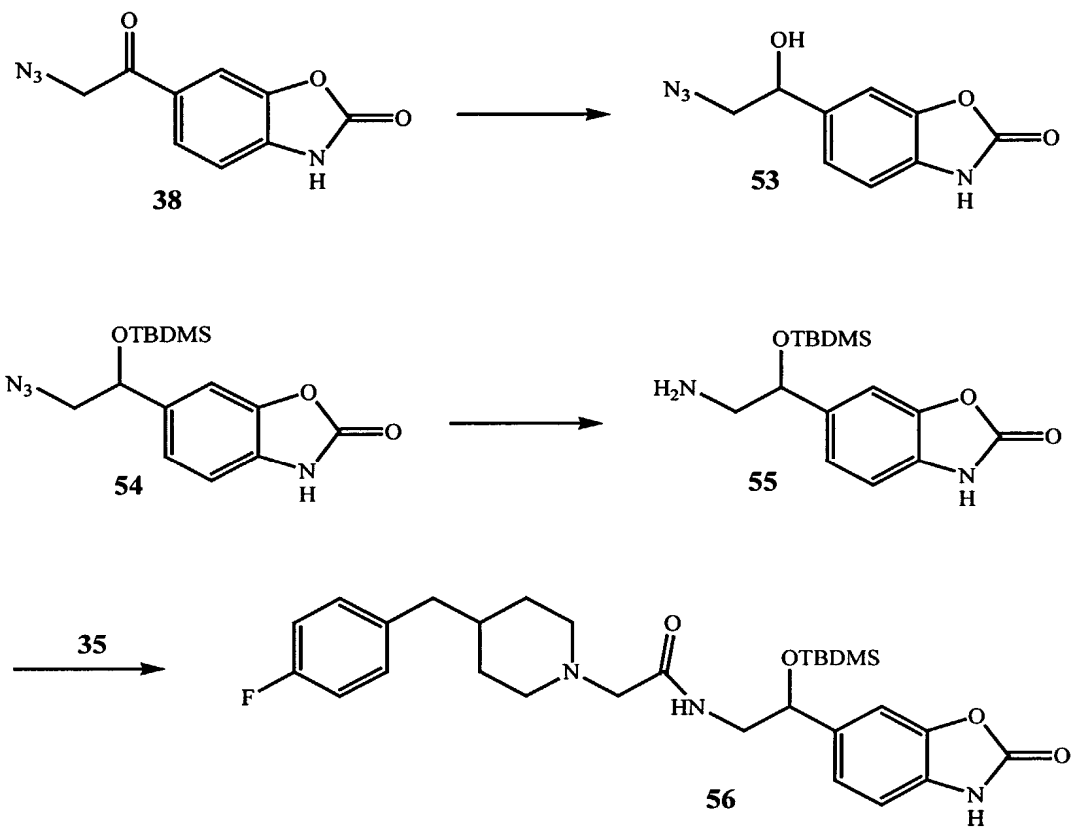
ν_{\max} 3261, 1777, 1494, 1447, 1273 cm⁻¹

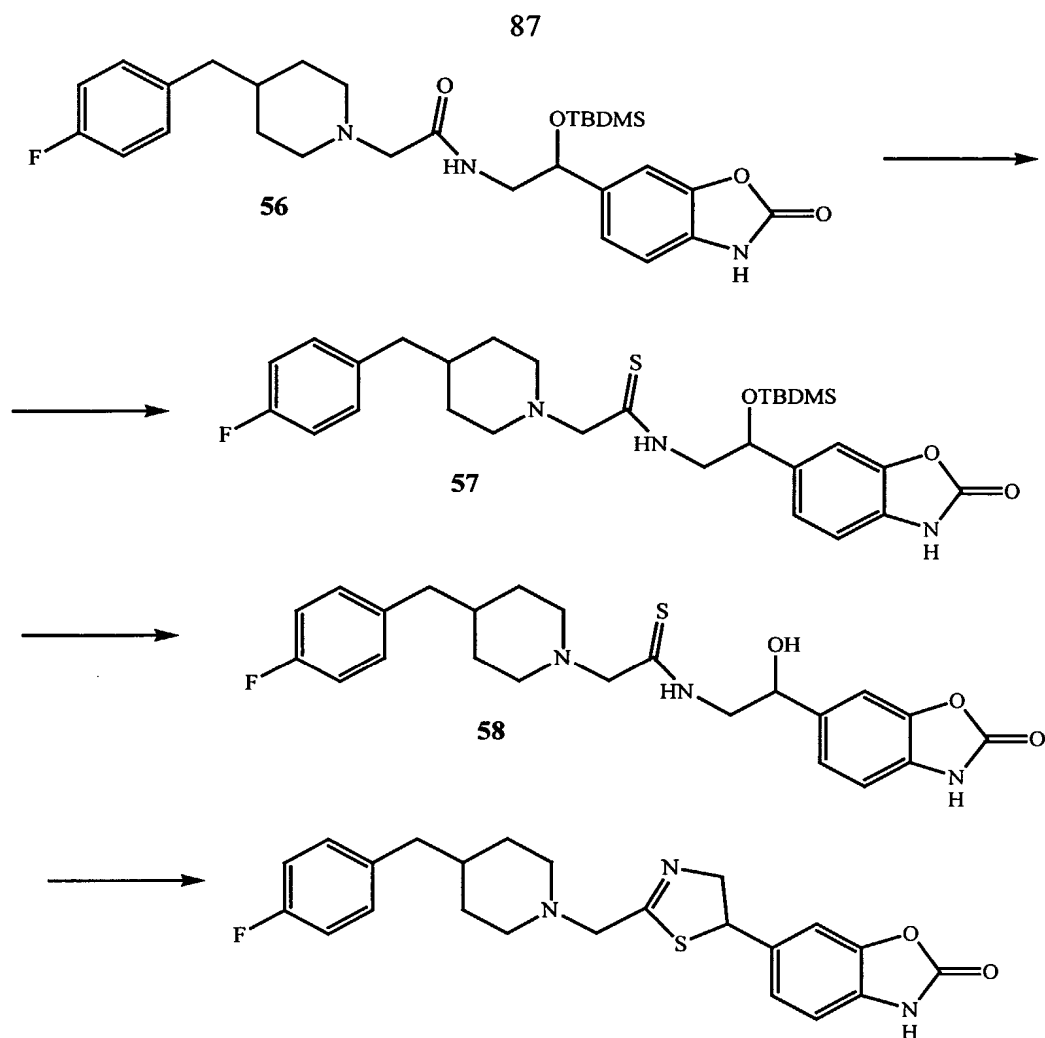
- 25 ¹H-NMR (CDCl₃) δ_H 1.31 (4H, m, alkyl), 1.60 (3H, m, alkyl), 1.97 (2H, t, CH₂, J 7.2 Hz), 2.53 (4H, 2 \times d, alkyl, J 6.4, 7.2 Hz), 2.90 (2H, bs, alkyl), 4.12 (1H, m, CHS), 4.35 (2H, m, CH₂N), 7.03 (1H, d, arom., J 8.0 Hz), 7.13-7.30 (5H, m, Ph), 7.62 (1H, dd, arom., J 1.6, 8.0 Hz), 7.73 (1H, d, arom., J 1.6 Hz).

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EXAMPLE 14

6-[2-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydrothiazol-5-yl]-3*H*-benzoxazol-2-one





Step 1: Sodium borohydride (603 mg, 15.46 mmol) was added to a solution of **38** (3.37 g, 15.46 mmol) in EtOH-MeOH (50-50 mL) at 0°C and stirred and allowed to warm to room temperature over 1 hour. The solvent was removed and the mixture diluted with EtOAc, washed with brine and dried (MgSO₄) to give **53** (2.09 g, 61%) as an orange/brown solid:

m/z 219.07 (M-H)⁻

ν_{\max} 3258, 2105, 1758 cm⁻¹

NMR δ_{H} (DMSO-d₆) 3.34 (2H, ddd, CH₂, J 4.0, 7.6, 12.8 Hz), 4.80 (1H, ddd, CHO, J 3.6, 4.4, 7.2 Hz), 5.48 (1H, d, OH, J 4.8 Hz), 7.04 (1H, d, arom., J 8.0 Hz), 7.17 (1H, dd, arom., J 0.8, 7.6 Hz), 7.30 (1H, s, arom.), 11.60 (1H, bs, NH).

Step 2: 2,6-Lutidine (1.02 g, 9.5 mmol) was added to a solution of **53** (2.09 g, 9.5 mmol) in THF (50 mL) at 0°C, followed by TBDMSOTf (2.51 g, 9.50 mmol) and the solution allowed to warm to room temperature. After 2 hours, a further aliquot of TBDMSOTf (1.25 g, 4.75 mmol) was added and the solution stirred for
5 a further 1 hour. The mixture was diluted with EtOAc, washed with saturated NaHCO₃, 10% HCl, brine and dried (MgSO₄). The material was partially purified by chromatography (silica gel, 0-30% EtOAc in heptane) to yield **54** (3.20 g, quantitative) as a yellow oil:

m/z 449.24 (M+TBDMS+H⁺)

10 *v*_{max} 3227, 2102, 1771, 1260, 838 cm⁻¹

NMR δ_H (DMSO-d₆) 0.10 (3H, SiCH₃), 0.10 (3H, s, SiCH₃), 0.87 (9H, s, Si^tBu), 3.32 (2H, m, CH₂), 4.97 (1H, dd, CHO, *J* 3.6, 6.8 Hz), 7.06 (1H, d, arom., *J* 7.6 Hz), 7.18 (1H, dd, arom., *J* 1.2 8.0 Hz), 7.29 (1H, s, arom.), 11.62 (1H, bs, NH).

15 **Step 3:** Compound **54** (3.20 g, 9.5 mmol assumed) and 10% Pd-C (400 mg) in MeOH (50 mL) were hydrogenated at 50 psi and 30°C for 2 hours. The mixture was filtered through Kieselguhr, the filter cake was then washed with DMF (~300 mL), and these washings were concentrated to yield **55** (1.81 g, 62%) as an off-white solid:

20 *m/z* 309.18 (MH⁺)

*v*_{max} 3418, 1677, 1582, 1263 cm⁻¹

NMR δ_H (DMSO-d₆) 0.12 (3H, SiCH₃), 0.05 (3H, s, SiCH₃), 0.85 (9H, s, Si^tBu), 2.62 (1H, dd, CH₂, *J* 5.2, 6.4 Hz), 4.62 (1H, dd, CHO, *J* 5.2, 6.4 Hz), 7.01 (1H, d, arom., *J* 8.0 Hz), 7.06 (1H, dd, arom., *J* 1.6 8.0 Hz), 7.17 (1H, s, arom.).

25 **Step 4:** Compound **35** (1.69 g, 5.88 mmol), HBTU (2.29 g, 5.88 mmol) and DIPEA (3.03 g, 23.51 mmol) in DMF (25 mL) were stirred at room temperature for 10 minutes, then **55** (1.81 g, 5.88 mmol) was added, and the mixture stirred at room temperature for 4 hours. The solvent was removed and the mixture taken up in EtOAc, washed with saturated NaHCO₃, brine and dried (MgSO₄). The

product was purified by chromatography (silica gel, 0-5% MeOH in CH₂Cl₂) to yield **56** (1.32 g, 42%) as a fawn colored foam:

m/z 542.30 (MH⁺)

*v*_{max} 3351, 1778, 1657, 1509 cm⁻¹

- 5 ¹H-NMR (CDCl₃) δ_H 0.09 (3H, SiCH₃), 0.08 (3H, s, SiCH₃), 0.94 (9H, s, Si^tBu), 1.27 (2H, m, alkyl), 1.58 (3H, m, alkyl), 2.04 (1H, t, CH, *J* 11.2 Hz), 2.18 (1H, t, CH, *J* 10.8 Hz), 2.51 (2H, d, CH₂, *J* 6.8 Hz), 2.75 (2H, m, alkyl), 2.92 (2H, m, alkyl), 3.28 (1H, m, alkyl), 3.56 (1H, m, alkyl), 4.82 (1H, dd, CHO, *J* 4.4, 6.0 Hz), 6.91-7.00 (3H, m, arom.), 7.09 (3H, m, arom.), 7.22 (1H, s, arom.), 7.56 (1H, bm, CONH), 8.36 (1H, bs, NH).
- 10

- Step 5:** Compound **56** (1.32 g, 2.44 mmol) and Lawesson's reagent (493 mg, 1.22 mmol) in dioxane (10 mL) were stirred and heated to reflux for 1.5 hours. A further aliquot of Lawesson's reagent (493 mg, 1.22 mmol) was added and heating continued for 1 hour. The mixture was diluted with EtOAc, washed with saturated NaHCO₃, brine and dried (MgSO₄). The crude material was purified by chromatography (silica gel, 0-50% EtOAc/heptane) to give **57** (806 mg, 59%) as a cream colored oil which solidified on standing:
- 15

m/z 557.31 (MH⁺)

*v*_{max} 3250, 1776, 1509, 1259, 836 cm⁻¹

- 20 ¹H-NMR (CDCl₃) δ_H 0.07 (3H, SiCH₃), 0.07 (3H, s, SiCH₃), 0.90 (9H, s, Si^tBu), 1.18 (2H, m, alkyl), 1.47-1.65 (3H, m, alkyl), 2.04 (1H, dt, CH, *J* 2.2, 11.6 Hz), 2.22 (1H, dt, CH, *J* 2.2, 11.6 Hz), 2.51 (2H, d, CH₂, *J* 6.8 Hz), 2.57 (1H, d, CHH, *J* 12.0 Hz), 2.72 (1H, d, CHH, *J* 12.0 Hz), 3.40 (2H, dd, CH₂, *J* 17.6, 25.2 Hz), 3.80 (1H, m, alkyl), 4.03 (1H, m, alkyl), 5.09 (1H, dd, CHO, *J* 4.0, 6.0 Hz), 6.98 (3H, m, arom.), 7.09 (2H, m, arom.), 7.16 (1H, d, arom., *J* 8.0 Hz), 7.29 (1H, s, arom.), 7.90 (1H, s, CONH), 9.56 (1H, bs, NH).
- 25

Step 6: Compound **57** (806 mg, 1.45 mmol) in THF (10 mL) was treated with TBAF (1 M in THF, 2.90 mL, 2.90 mmol) and stirred at room temperature for 4 hours. The mixture was diluted with EtOAc, washed with 10% citric acid,

saturated NaHCO₃, brine and dried (MgSO₄). The product was purified by chromatography (silica gel, 0-2% MeOH/CH₂Cl₂) to give **58** as a fawn colored foam (348 mg, 64%):

m/z 444.19 (MH⁺)

5 *v*_{max} 3210, 1766, 1509 cm⁻¹

¹H-NMR (CDCl₃) δ_H 1.15 (2H, m, alkyl), 1.49-1.61 (3H, m, alkyl), 2.15 (2H, t, alkyl, *J* 12.0 Hz), 2.49 (2H, d, CH₂, *J* 7.2 Hz), 2.68 (2H, t, CH₂, *J* 12.4 Hz), 2.76 (1H, bs, OH), 3.44 (2H, dd, CH₂, *J* 18.0, 19.2 Hz), 3.76 (1H, dd, CHH, *J* 8.0, 14.0 Hz), 4.25 (1H, dd, CHH, *J* 2.8, 14.0 Hz), 5.13 (1H, dd, CHO, *J* 3.2, 7.2 Hz),
10 6.95-7.00 (2H, m, arom.), 7.03-7.09 (3H, m, arom.), 7.22 (1H, d, arom., *J* 8.4 Hz), 7.33 (1H, s, arom.), 9.69 (1H, bs, NH).

Step 7: Compound **58** (348 mg, 786 μmol) and Burgess reagent (187 mg, 786 μmol) in THF (10 mL) were stirred and heated to reflux for 4 hours. An aliquot of Burgess Reagent (37 g, 157 μmol) was added and heating continued for
15 a further 2 hours. Diluted with EtOAc, washed with saturated NaHCO₃, brine and dried (MgSO₄). The product was purified by chromatography (silica gel, 0-2% MeOH/CH₂Cl₂) and then again using (silica gel, 0-75% EtOAc/heptane) to yield 6-{2-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydrothiazol-5-yl}-3*H*-benzoxazol-2-one (98 mg, 29%) as a white solid:

20 *m/z* 426.26 (MH⁺)

*v*_{max} 3111, 1771, 1622, 1509, 1219 cm⁻¹

¹H-NMR (CDCl₃) δ_H 1.34 (2H, m, alkyl), 1.49 (1H, m, alkyl), 1.59 (2H, m alkyl), 2.06 (2H, dd, alkyl, *J* 9.6, 19.2 Hz), 2.50 (2H, d, CH₂, *J* 7.2 Hz), 2.93 (2H, dd, CH₂, *J* 10.8, 10.8 Hz), 3.39 (2H, dd, CH₂, *J* 16.2, 16.2 Hz), 4.37 (1H, dd, CHH, *J* 4.8, 15.6 Hz), 4.58 (1H, dd, CHH, *J* 9.2, 16.0 Hz), 4.87 (1H, dd, CHO, *J* 5.2, 9.2 Hz), 6.94 (3H, m, arom.), 7.06 (3H, m, arom.), 7.15 (1H, d, arom., *J* 1.2 Hz), 8.41 (1H, bs, NH).

25

General Methods for Examples 15-36:

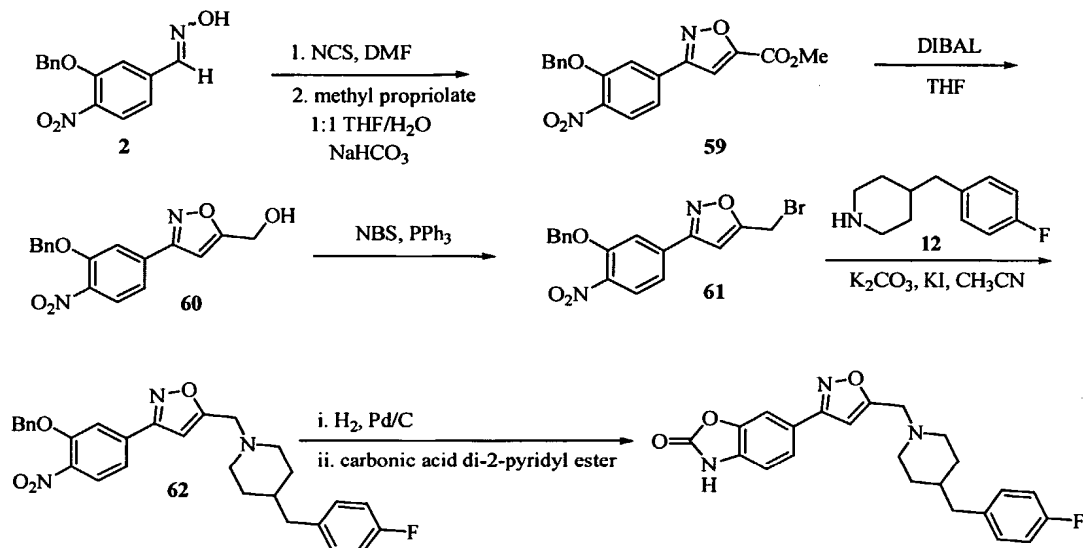
HCl salts were prepared by treatment of a MeOH solution of the amine with excess HCl in Et₂O (1 M). The salts were isolated either by filtration if they precipitated directly from the etherial solution, or by first removal of the solvent under reduced pressure, and then crystallization (Et₂O/MeOH).

Purity was determined by reversed phase HPLC by the following methods:

- Method A: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4 μ; solvent A: 0.1% H₃PO₄ in 95:5 H₂O/CH₃CN; solvent B: 0.1% H₃PO₄ in 95:5 CH₃CN/H₂O; gradient: 10-100% B over 15 minutes; flow: 1 mL min⁻¹; detection: 210 nm.
- Method B: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4 μ; solvent A: 0.1% H₃PO₄ in 95:5 H₂O/MeOH; solvent B: 0.1% H₃PO₄ in 95:5 MeOH/H₂O; gradient: 10-100% B over 15 minutes; flow: 1 mL min⁻¹; detection: 215 nm.
- Method C: column: SYNERGI MAX-RP C12, 80 Å, 150 × 4.6 mm, 4 μ; solvent A: 95:5 H₂O/ CH₃CN; solvent B: 95:5 CH₃CN/H₂O; gradient: 10-100% B over 15 minutes; flow: 1 mL min⁻¹; detection: 215 nm.
- Method D: column: SYNERGI MAX-RP C12, 80 Å, 150 × 4.6 mm, 4 μ; solvent A: 95:5 H₂O/MeOH; solvent B: 95:5 MeOH/H₂O; gradient: 10-100% B over 15 minutes; flow: 1 mL min⁻¹; detection: 215 nm.

EXAMPLE 15

6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]isoxazol-3-yl}-3*H*-benzoxazol-2-one



- 5 **Step 1:** A solution of oxime of formula 2 (8.41 g, 30.9 mmol) and freshly crystallized (benzene) *N*-chlorosuccinimide (4.12 g, 30.9 mmol) in DMF (30 mL) was stirred at room temperature for 1 hour. The reaction was partitioned between EtOAc and H₂O. The organic layer was washed with saturated NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was dissolved in
- 10 1:1 THF/H₂O (30 mL). Sodium bicarbonate (7.80 g, 92.7 mmol) and methyl propiolate (2.4 mL, 40.2 mmol) were added, and the reaction mixture was stirred overnight. The reaction was diluted with EtOAc and the organic layer was dried (Na₂SO₄), and concentrated under reduced pressure. Ester of formula 59 (7.21 g, 66%) was isolated as a yellow solid following trituration with EtOAc/hexanes:
- 15 ¹H NMR (500 MHz, CDCl₃): δ 7.96 (d, *J* 9 Hz, 1H), 7.70 (d, *J* 2 Hz, 1H), 7.48 (dd, *J* 8, 1 Hz, 2H), 7.42-7.39 (m, 3H), 7.36-7.33 (m, 1H), 7.25 (s, 1H), 5.32 (s, 2H), 4.01 (s, 3H).

Step 2: To an ice-cold solution of the ester of formula 59 (7.21 g, 20.3 mmol) in THF (100 mL) was added diisobutylaluminum hydride (51.0 mL of a 1.0 M solution in cyclohexane, 51.0 mmol). After 1 hour, the reaction was diluted with MeOH (2 mL) and a saturated solution of Rochelle's salt (50 mL) was added.

20

After stirring briefly, the solution became gel like. The gel dissolved upon addition of EtOAc (150 mL) and the solution was stirred for several hours. The organic layer was washed with H₂O and saturated NaCl, dried (Na₂SO₄) and concentrated under reduced pressure to give the alcohol of formula **60** (6.57 g, 99%) as a yellow solid:

¹H NMR (300 MHz, CDCl₃): δ 7.96 (d, *J* 9 Hz, 1H), 7.70 (d, *J* 2 Hz, 1H), 7.49 (dd, *J* 8, 1 Hz, 2H), 7.42-7.30 (m, 4H), 6.60 (s, 1H), 5.32 (s, 2H), 4.85 (s, 2H), 2.15 (s, 1H).

Step 3: Triphenylphosphine (6.56 g, 25.0 mmol) and *N*-bromosuccinimide (4.45 g, 25.0 mmol) were added to an ice-cold solution of alcohol of formula **60** (6.53 g, 20.0 mmol) in THF (50 mL) and the solution was stirred for 1 hour. The mixture was partitioned between EtOAc and saturated NaHCO₃. The organic layer was washed with saturated NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. Purification by chromatography (silica gel, 1:4 hexanes/EtOAc) gave bromide of formula **61** (6.88 g, 88%):

¹H NMR (500 MHz, CDCl₃): δ 7.94 (d, *J* 8 Hz, 1H), 7.67 (d, *J* 2 Hz, 1H), 7.49 (dd, *J* 8, 1 Hz, 2H), 7.42-7.34 (m, 4H), 6.62 (s, 1H), 5.30 (s, 2H), 4.51 (s, 2H).

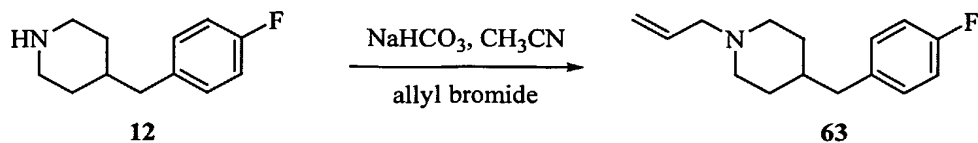
Step 4: A solution of bromide of formula **61** (3.42 g, 8.79 mmol), amine of formula **12** (2.01 g, 8.79 mmol), K₂CO₃ (2.41 g, 17.5 mmol), KI (146 mg, 0.879 mmol), and LiBr (200 mg, 2.30 mmol) in CH₃CN (30 mL) was stirred at 50°C overnight. The reaction solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The organic layer was washed with saturated NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. Purification by chromatography (silica gel, 99:1 to 95:5 CH₂Cl₂/MeOH) gave compound of formula **62** (3.26 g, 74%) as a pale yellow oil:

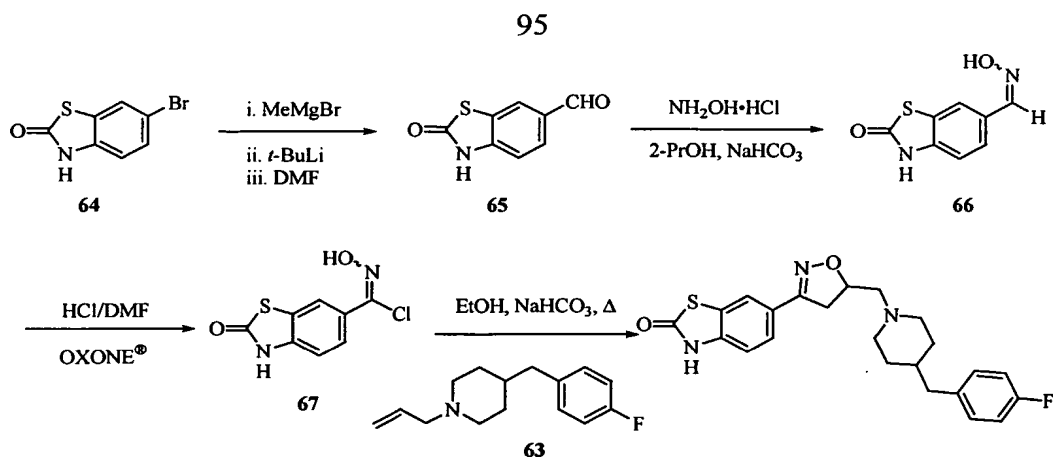
¹H NMR (300 MHz, CDCl₃): δ 7.94 (d, *J* 8 Hz, 1H), 7.67 (d, *J* 2 Hz, 1H), 7.49 (dd, *J* 8, 1 Hz, 2H), 7.42-7.30 (m, 4H), 7.08 (dd, *J* 8, 7 Hz, 2H), 6.95 (dd, *J* 8, 7 Hz, 2H), 6.50 (s, 1H), 5.32 (s, 2H), 3.73 (s, 2H), 2.92 (d, *J* 12 Hz, 2H), 2.51 (d, *J* 7 Hz, 2H), 2.08 (ddd, *J* 12, 12, 2 Hz, 2H), 1.67-1.25 (m, 5H).

- Step 5:** Palladium on charcoal (10% Pd, 200 mg) was added to a solution of compound of formula **62** (2.42 g, 4.80 mmol) in THF (100 mL), and the mixture was shaken under an atmosphere of H₂ (g) at 50 psi for 4 hours. The reaction mixture was rapidly filtered through CELITE under reduced pressure into a
- 5 reaction flask. The flask was capped with a septum and purged with nitrogen. To the clear solution was added carbonic acid di-2-pyridyl ester (1.15 g, 5.28 mmol) and Et₃N (1.50 mL, 10.56 mmol), and the solution was refluxed for 6 hours. The solvent was removed under reduced pressure. Purification by chromatography (silica gel, 99:1 to 95:5 CH₂Cl₂/MeOH) and subsequent crystallization from hot
- 10 EtOH gave 6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]isoxazol-3-yl}-3*H*-benzoxazol-2-one (665 mg, 34%) as an off-white solid:
mp 237-244°C
- IR (KBr): 2934, 2825, 1775 cm⁻¹;
- ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.87 (s, 1H), 7.78 (d, *J* 1 Hz, 1H), 7.70 (dd, *J* 8, 1 Hz, 1H), 7.20-7.15 (m, 3H), 7.07 (dd, *J* 8, 7 Hz, 2H), 6.93 (s, 1H), 3.66 (s, 2H), 2.84 (d, *J* 11 Hz, 2H), 2.47 (d, *J* 6 Hz, 2H), 1.99 (dd, *J* 11, 10 Hz, 2H), 1.54-1.45 (m, 3H), 1.25-1.18 (m, 2H); ESI -MS
- (*m/z*): 408 [M + H]⁺; HPLC: method A, 5.91 minutes(>99%); method B, 11.23 minutes(>99%); Anal. Calcd for C₂₃H₂₂FN₃O₃: C, 67.80; H, 5.44; N, 10.31.
- 20 Found: C, 67.67; H, 5.52; N, 10.11.

EXAMPLE 16

6-{5-[4-(4-Fluorobenzyl)piperidin-1-yl]methyl}-4,5-dihydroisoxazol-3-yl}-3*H*-benzothiazol-2-one





Step 1: 4-(4-Fluorobenzyl)piperidine hydrochloride **12** (2.55 g, 11.1 mmol) and NaHCO₃ (2.3 g, 27.7 mmol) were added to a solution of allyl bromide in CH₃CN.

The mixture was warmed to 40°C for 3 hours. The solvent was removed under

5 reduced pressure and the residue was partitioned between EtOAc and water. The organic layer was washed with saturated NaCl, dried (Na₂SO₄), filtered, and the solvent removed under reduced pressure. Purification by flash chromatography (silica gel, 95:5 to 9:1 CH₂Cl₂/MeOH) gave alkene of formula **63** (1.13 g, 44%) as an oil:

10 ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.18-7.14 (m, 2H), 7.08-7.03 (m, 2H), 5.81-5.73 (m, 1H), 5.11 (dd, *J* 17, 2 Hz, 1H), 5.06 (dd, *J* 11, 2 Hz, 1H), 2.87 (d, *J* 6 Hz, 2H), 2.77 (d, *J* 12 Hz, 2H), 2.47 (d, *J* 7 Hz, 2H), 1.79 (dt, *J* 12, 2 Hz, 2H), 1.50-1.39 (m, 3H), 1.15 (tt, *J* 13, 3 Hz, 2H).

Step 2: To a -78°C solution of bromide of formula **64** (5.02 g, 21.8 mmol) in THF

15 (50 mL) was added MeMgBr (8.0 mL of a 3.0 M solution in diethyl ether, 24.0 mmol). After 30 minutes, anhydrous THF (170 mL) was added at a rate that maintained the internal reaction temperature below a threshold of -50°C. After the solution returned to -78°C, *tert*-butyl lithium (50 mL of a 1.7 M solution in pentane, 85 mmol) was added. After 10 minutes, DMF (10 mL, 130 mmol) was

20 added to the yellow mixture, and the cold bath was removed. After 1 hour, the reaction was quenched with water, and the THF was removed under reduced pressure. The residue was partitioned between EtOAc and 1N HCl. The aqueous layer was extracted with three portions of EtOAc. The organic extracts were

combined and washed with saturated NaCl, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give aldehyde of formula **65** (3.74 g, 96%) as a white solid:

¹H NMR (500 MHz, DMSO-*d*₆): δ 12.39 (s, 1H), 9.90 (s, 1H), 8.17 (d, *J* 1 Hz, 1H), 7.85 (dd, *J* 8, 1 Hz, 1H), 7.30 (d, *J* 8 Hz, 1H).

Step 3: A mixture of aldehyde of formula **65** (3.74 g, 20.8 mmol), hydroxylamine hydrochloride (1.60 g, 22.9 mmol), and sodium bicarbonate (2.18 g, 26.0 mmol) in 2-PrOH (75 mL) was heated to 75°C for 3 hours. After stirring overnight at room temperature, the mixture was diluted with 2-PrOH (200 mL). The solution was filtered and concentrated under reduced pressure to give oxime of formula **66** (4.00 g, 99%), as a white solid:

¹H NMR (300 MHz, DMSO-*d*₆): δ 11.96 (s, 1H), 11.15 (s, 1H), 8.10 (s, 1H), 7.79 (d, *J* 1 Hz, 1H), 7.52 (dd, *J* 8, 1 Hz, 1H), 7.14 (d, *J* 8 Hz, 1H).

Step 4: A mixture of oxime of formula **66** (4.00 g, 20.6 mmol) and OXONE® (13.9 g, 22.6 mmol) was stirred in a solution of HCl in DMF (43 mL of a 0.53 M, 22.6 mmol) for 3.5 hours. The reaction mixture was partitioned between EtOAc and 1N HCl. The organic layer was washed with saturated NaCl, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The yellow solid was triturated with 1:1 EtOAc/hexanes and filtered to give compound of formula **67** (3.53 g, 75%):

¹H NMR (300 MHz, DMSO-*d*₆): δ 12.33 (s, 1H), 12.15 (s, 1H), 8.03 (d, *J* 2 Hz, 1H), 7.73 (dd, *J* 8, 2 Hz, 1H), 7.20 (d, *J* 8 Hz, 1H).

Step 5: Coupling of compound of formula **67** and alkene of formula **63** following the procedure described in Example 17, Step 5, followed by conversion to the HCl salt, gave 6-{5-[4-(4-fluorobenzyl)piperidin-1-yl]methyl}-4,5-dihydroisoxazol-3-yl}-3*H*-benzothiazol-2-one (484 mg, 41%):

mp 271-276 °C

IR (KBr): 3422, 2932, 1686, 1670, 1603 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆): δ 12.19 (s, 1H), 10.58 (s, 1H), 7.88 (s, 1H), 7.60 (d, *J* 8 Hz, 1H), 7.23-7.20 (m, 3H), 7.11 (dd, *J* 9, 8 Hz, 2H), 5.30-5.24 (m, 1H),

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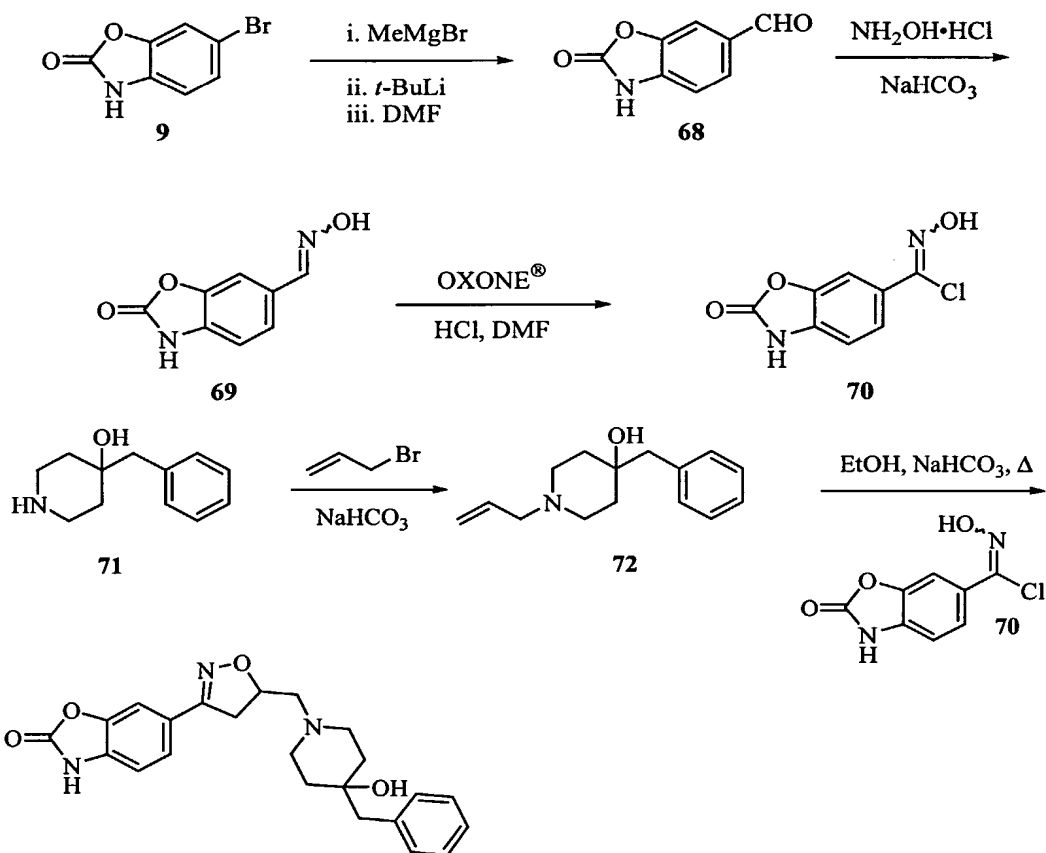
3.66 (dd, *J* 17, 11 Hz, 1H), 3.58 (d, *J* 12 Hz, 1H), 3.48 (d, *J* 11 Hz, 1H), 3.34-3.17 (m, 3H), 2.95 (m, 2H), 2.53 (d, *J* 5 Hz, 2H), 1.75-1.74 (m, 3H), 1.64-1.54 (m, 2H);

ESI-MS (*m/z*): 426 [*M* + *H*]⁺; HPLC: method A, 6.05 minutes (>99%); method B, 11.48 minutes (>99%); Anal. Calcd for C₂₃H₂₄FN₃O₂S·HCl·0.25H₂O: C,

5 59.22; H, 5.51; N, 9.01. Found: C, 59.37; H, 5.38; N, 8.82.

EXAMPLE 17

6-[5-(4-Benzyl-4-hydroxypiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one



Step 1: To a -78°C solution of **9** (20.0 g, 93.4 mmol) in THF (180 mL) was added MeMgBr (34.5 mL of a 3.0 M solution in diethyl ether, 103 mmol). After 45 minutes, anhydrous THF (750 mL) was added at a rate that maintained the internal reaction temperature below a threshold of -50°C. After the solution returned to -78°C, *tert*-butyl lithium (200 mL of a 1.7 M solution in pentane, 118 mmol) was added *via* a dropping funnel. After 15 minutes, DMF (44 mL,

561 mmol) was added to the yellow mixture, and the cold bath was removed. After 2 hours, the reaction was quenched with water and the THF removed under reduced pressure. The residue was partitioned between EtOAc and 1N HCl. The aqueous layer was extracted with EtOAc (2×). The combined organic extracts were washed with sat. NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. The crude solid was dissolved in hot EtOAc and hexane was added to the solution until a precipitate formed. The precipitate was collected by filtration to give **68** (12.44 g, 81%) as an off-white solid:

¹H NMR (500 MHz, DMSO-*d*₆): δ 12.13 (s, 1H), 9.92 (s, 1H), 7.78 (d, *J* 8 Hz, 1H), 7.75 (s, 1H), 7.29 (d, *J* 8 Hz, 1H).

Step 2: A mixture of aldehyde **68** (10.0 g, 61.3 mmol), hydroxylamine hydrochloride (4.26 g, 61.3 mmol), and sodium bicarbonate (5.15 g, 61.3 mmol) in 2-PrOH (75 mL) was heated to 40°C for 3 hours. After cooling to ambient temperature, the mixture was diluted with 2-PrOH and filtered. Concentration under reduced pressure gave oxime **69** (11.6 g, 100%), as a white solid:

¹H NMR (300 MHz, DMSO-*d*₆): δ 11.82 (s, 1H), 11.15 (s, 1H), 8.14 (s, 1H), 7.49 (s, 1H), 7.39 (d, *J* 8 Hz, 1H), 7.12 (d, *J* 8 Hz, 1H).

Step 3: A mixture of oxime **69** (11.6 g, 61.3 mmol) and OXONE® (41.4 g, 67.4 mmol) was stirred in HCl (62 mL of a 1.09 M solution in DMF, 67.4 mmol) for 2.5 hours. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (2×). The combined organic extracts were washed with sat. NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. Trituration of the yellow solid with EtOAc gave **70** (7.03 g, 54%). The washings were concentrated under reduced pressure and the residue trituated with 3:1 EtOAc/hexanes to give a second crop of **70** (2.34 g, 18%):

¹H NMR (300 MHz, DMSO-*d*₆): δ 12.33 (s, 1H), 11.93 (s, 1H), 7.63 (s, 1H), 7.60 (d, *J* 8 Hz, 1H), 7.18 (d, *J* 8 Hz, 1H).

Step 4: Alkene of formula **72** was prepared following the procedure described below for alkene of formula **63** in Example 16, Step 1, to give 420 mg, (14%): ¹H NMR (500 MHz, CDCl₃): δ 7.30 (dd, *J* 8, 7 Hz, 2H), 7.24-7.23 (m, 1H), 7.19 (d, *J*

7 Hz, 2H), 5.91-5.83 (m, 1H), 5.17 (dd, *J* 17, 2 Hz, 1H), 5.12 (dd, *J* 10, 2 Hz, 1H), 3.01 (d, *J* 6 Hz, 2H), 2.75 (s, 2H), 2.67-2.63 (m, 2H), 2.28 (dt, *J* 10, 2 Hz, 2H), 1.74 (dt, *J* 13, 4 Hz, 2H), 1.53 (dd, *J* 14, 2 Hz, 2H), 1.17 (s, 1H).

Step 5: A solution of alkene of formula **72** (420 mg, 1.81 mmol) in EtOH (10 mL)

- 5 was added to a mixture of NaHCO₃ and compound of formula **70** (425 mg, 2.0 mmol). The mixture was heated to reflux for 2 hours. Methanol and CH₂Cl₂ were added to dissolve an organic precipitate that had formed during the course of the reaction. Silica gel was added and the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, 89:10:1
- 10 CH₂Cl₂/MeOH/NH₄OH), trituration of the isolated solid with MeOH, and conversion to the HCl salt gave IUPAC: 6-[5-(4-benzyl-4-hydroxypiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one (425 mg, 52%) as a white solid:
- mp 166-170°C

- 15 IR (KBr): 3387, 2958, 1773 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆): δ 12.01 (s, 1H), 10.20 (s, 1H), 7.57 (s, 1H), 7.47 (d, *J* 8 Hz, 1H), 7.30 (dd, *J* 8, 7 Hz, 2H), 7.24 (d, *J* 7 Hz, 2H), 7.14 (d, *J* 8 Hz, 2H), 5.23 (m, 1H), 4.82 (s, 1H), 3.66 (dd, *J* 17, 11 Hz, 1H), 3.37-3.33 (m, 4H), 3.19-3.16 (m, 2H), 2.74 (s, 2H), 1.93-1.85 (m, 2H), 1.61 (d, *J* 15 Hz, 2H); ESI-MS

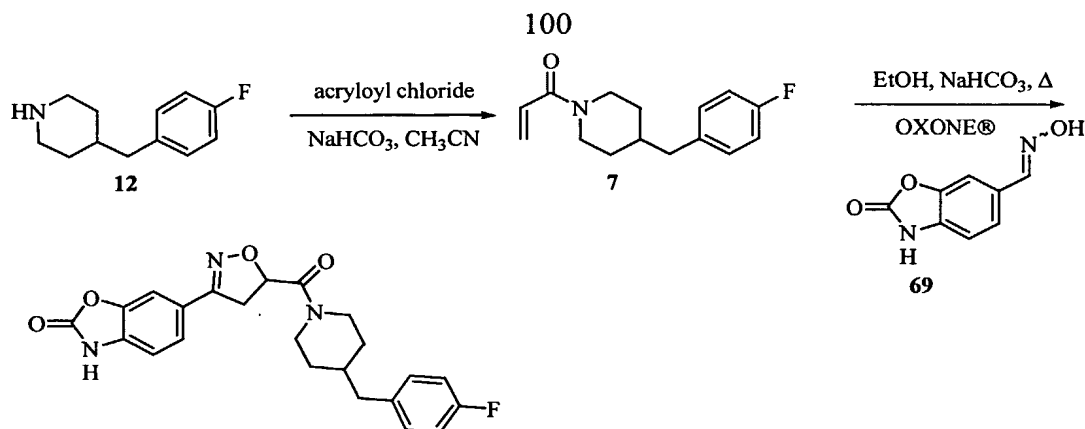
- 20 (*m/z*): 408 [M + H]⁺

HPLC: method A, 4.14 minutes (98.2%); method B, 9.92 minutes (>99%); Anal.

Calcd for C₂₃H₂₅N₃O₄·1.125 H₂O: C, 59.22; H, 6.08; N, 9.01. Found: C, 59.34; H, 5.94; N, 8.96.

EXAMPLE 18

- 25 6-{5-[4-(4-Fluorobenzyl)piperidine-1-carbonyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one



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Purification by flash chromatography (silica, 5:2 hexanes/EtOAc to 9:1 CH₂Cl₂/MeOH) followed by trituration with 3:1 hexanes/EtOAc gave 6-{5-[4-(4-fluorobenzyl)piperidine-1-carbonyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (507 mg, 40%):

5 mp 210-213°C

IR (KBr): 3193, 2931, 1779, 1632 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆): δ 11.84 (s, 1H), 7.59 (s, 1H), 7.50 (d, *J* 8 Hz, 1H), 7.23-7.20 (m, 2H), 7.16 (d, *J* 8 Hz, 1H), 7.10 (dd, *J* 9, 8 Hz, 2H), 5.58-5.51 (m, 1H), 4.35-4.30 (m, 1H), 4.03 (d, *J* 14 Hz, 1H), 3.90-3.77 (m, 1H), 3.54-3.47 (m, 1H), 3.09-3.00 (m, 1H), 2.64-2.58 (m, 1H), 2.54 (d, *J* 7 Hz, 2H), 1.79 (m, 1H), 1.68-1.58 (m, 2H), 1.24-1.16 (m, 1H), 1.08-0.97 (m, 1H)

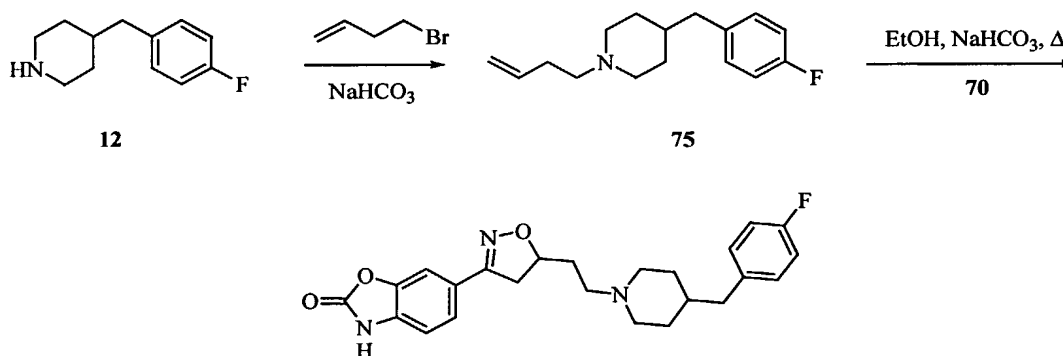
ESI-MS (*m/z*): 424 [M + H]⁺

HPLC: method A, 10.06 min (98.6%); Anal. Calcd for C₂₃H₂₂FN₃O₄: C, 65.24; H, 5.24; N, 9.92. Found: C, 65.03; H, 5.20; N, 9.87.

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EXAMPLE 19

6-(5-{2-[4-(4-Fluorobenzyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one



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3.43-3.38 (m, 2H), 3.18-3.14 (m, 1H), 3.04-3.00 (m, 2H), 2.85-2.78 (m, 2H), 2.52-2.47 (m, 3H), 1.80-1.68 (m, 3H), 1.59-1.51 (m, 2H).

Step 2: Coupling of **70** (156 mg, 0.734 mmol) and alkene **75** (207 mg, 0.734 mmol) following the procedure described in Example 17, Step 5, followed by conversion to the HCl salt, gave 6-(5-{2-[4-(4-fluorobenzyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one (200 mg, 58%):
mp 254-258°C

IR (KBr): 3448, 2934, 2713, 1774 cm⁻¹

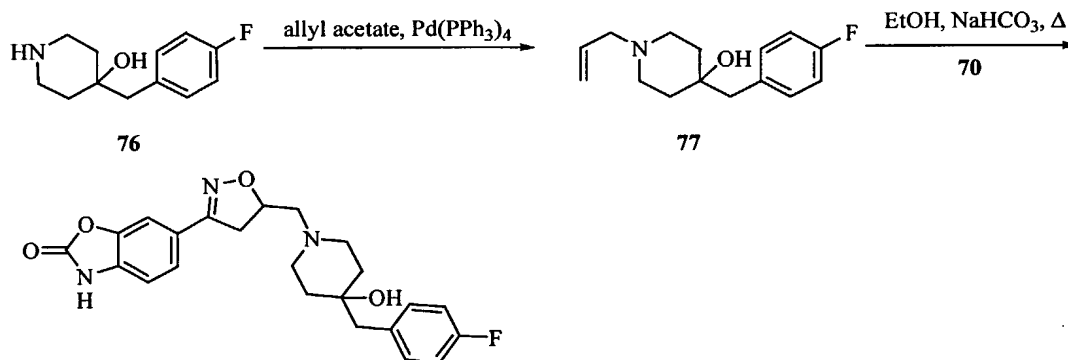
¹H NMR (500 MHz, DMSO-*d*₆): δ 11.90 (s, 1H), 10.09 (s, 1H), 7.55 (s, 1H), 7.46 (d, *J* 8 Hz, 1H), 7.21 (dd, *J* 9, 8 Hz, 2H), 7.16 (d, *J* 8 Hz, 1H), 7.11 (dd, *J* 9, 8 Hz, 2H), 4.79-4.73 (m, 1H), 3.54 (dd, *J* 17, 11 Hz, 1H), 3.45 (d, *J* 11 Hz, 2H), 3.18-3.09 (m, 4H), 2.83 (m, 2H), 2.53-2.49 (m, 2H), 2.06 (dd, *J* 15, 8 Hz, 2H), 1.73-1.70 (m, 2H), 1.52-1.48 (m, 2H)

ESI-MS (*m/z*): 424 [M + H]⁺

HPLC: method A, 5.69 min (98.0%); method B, 10.96 min (98.4%); Anal. Calcd for C₂₄H₂₆FN₃O₃·HCl·0.5H₂O: C, 61.47; H, 6.02; N, 8.96. Found: C, 61.59; H, 6.02; N, 9.87.

EXAMPLE 20

6-{5-[4-(4-Fluorobenzyl)-4-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one



Step 1: To a suspension of the formate salt of amine **76** (14.3 g, 43.4 mmol) in toluene (225 mL) was added allyl acetate (5.2 mL, 47.7 mmol) and Et₃N (12.1 mL, 86.8 mmol). Solubility of the amine was problematic. Addition of

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pyridine (20 mL) and then MeOH (40 mL) resulted in a homogenous solution. The solution was deoxygenated with an argon sparge for 15 minutes, then palladium tetrakis(triphenylphosphine)palladium(0) (500 mg, 0.434 mmol) was added. The reaction mixture was heated to 100°C in an oil bath for 1 hour and then cooled to ambient temperature. The mixture was filtered and the solution concentrated under reduced pressure. Purification by chromatography (silica, 95:5 to 9:1 CH₂Cl₂/MeOH) gave **77** (7.15 g, 70%) as a clear oil:

¹H NMR (500 MHz, CDCl₃): δ 7.17 (dd, *J* 9, 8 Hz, 2H), 7.02 (dd, *J* 9, 8 Hz, 2H), 6.23-6.09 (m, 1H), 5.53-5.43 (m, 2H), 3.54 (d, *J* 7 Hz, 2H), 3.31-3.27 (m, 2H), 3.01 (br. t, *J* 11 Hz, 2H), 2.83 (s, 2H), 2.37 (dt, *J* 13, 4 Hz, 2H), 2.06 (s, 1H), 1.71 (br. d, *J* 13 Hz, 2H).

Step 2: Coupling of **70** (978 mg, 4.16 mmol) and alkene **77** (975 mg, 4.57 mmol) following the procedure described in Example 17, Step 5, followed by conversion to the HCl salt, gave 6-{5-[4-(4-fluorobenzyl)-4-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (840 mg, 43%): mp 195-204°C

IR (KBr): 3380, 2958, 1770, cm⁻¹

¹H NMR (500 MHz, CD₃OD): δ 7.58 (s, 1H), 7.52 (d, *J* 8 Hz, 1H), 7.29-7.24 (m, 2H), 7.15 (dd, *J* 8, 2 Hz, 1H), 7.06-7.00 (m, 2H), 5.28-5.23 (m, 1H), 3.71 (dd, *J* 17, 11 Hz, 1H), 3.52-3.20 (m, 6H), 2.83 (s, 2H), 2.03-1.90 (m 2H), 1.79-1.70 (m, 2H), 1.18 (dt, *J* 7, 2 Hz, 1H)

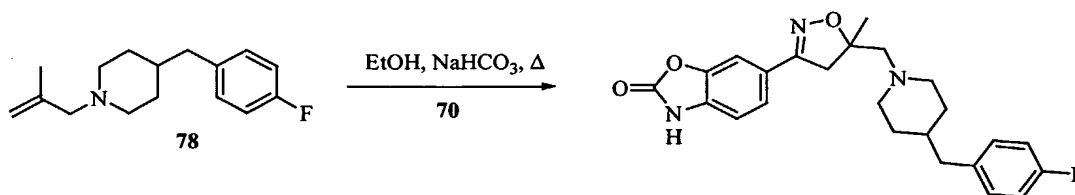
APCI-MS (*m/z*): 426 [M + H]⁺

HPLC: method A, 5.37 min (96.4%); method B, 10.38 min (98.3%); Anal. Calcd for C₂₃H₂₄FN₃O₄·HCl·0.5H₂O: C, 58.66; H, 5.56; N, 8.92. Found: C, 58.61; H, 5.60; N, 8.40.

EXAMPLE 21

6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one

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Step 1: A mixture of 4-(4-fluorobenzyl)piperidine hydrochloride (**12**) (3.05 g, 13.2 mmol) and NaHCO₃ (2.76 g, 32.8 mmol) in CH₃CN (50 mL) was heated to reflux for 30 minutes. After cooling to ambient temperature, methallyl bromide (1.7 mL, 17 mmol) was added, and the mixture was heated to reflux for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, 98:2 to 9:1 CH₂Cl₂/MeOH) gave **78** (2.67 g, 81%) as an oil:

¹H NMR (300 MHz, DMSO-*d*₆): δ 7.21-7.16 (m, 2H), 7.11-7.05 (m, 2H), 4.81 (m, 2H), 2.75-2.70 (m, 4H), 2.49 (m, 2H), 1.72 (m, 2H), 1.65 (s, 3H), 1.51-1.48 (m, 3H), 1.17-1.13 (m, 2H).

Step 2: Coupling of **70** (610 mg, 2.87 mmol) and alkene **78** (644 mg, 2.60 mmol) following the procedure described in Example 17, Step 5, gave 6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3H-benzoxazol-2-one (299 mg, 26%) as a white solid: mp 82-86°C

IR (KBr): 2925, 1774 cm⁻¹

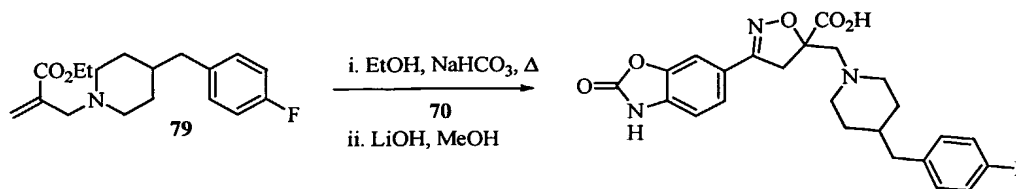
¹H NMR (500 MHz, DMSO-*d*₆): δ 11.79 (s, 1H), 7.54 (d, *J* 1 Hz, 1H), 7.43 (dd, *J* 8, 1 Hz, 1H), 7.17-7.12 (m, 3H), 7.05 (dd, *J* 9, 9 Hz, 2H), 3.38 (d, *J* 17 Hz, 1H), 3.17 (s, 2H), 3.07 (d, *J* 17 Hz, 1H), 2.90-2.88 (m, 2H), 2.44 (d, *J* 7 Hz, 2H), 2.07-1.97 (m, 2H), 1.49-1.36 (m, 3H), 1.29 (s, 3H), 1.20-1.06 (m, 2H)

APCI-MS (*m/z*): 424 [M + H]⁺

HPLC: method A, 6.57 min (97.8%); method B, 11.89 min (96.5%); Anal. Calcd for C₂₄H₂₆FN₃O₃·0.75H₂O: C, 65.96; H, 6.34; N, 9.62. Found: C, 66.03; H, 6.62; N, 9.25.

EXAMPLE 22

5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid



- Step 1:** To a suspension of the hydrochloride salt of amine **12** (2.06 g, 8.96 mmol) in toluene (50 mL) was added 2-acetoxymethylacrylic acid ethyl ester (1.70 g, 9.86 mmol) and Et₃N (1.37 mL, 9.86 mmol). The solution was deoxygenated with an argon sparge for 10 minutes, then palladium tetrakis(triphenylphosphine)-palladium(0) (260 mg, 0.224) was added. The reaction mixture was heated to 100°C in an oil bath for 1 hour, and then cooled to ambient temperature. The mixture was filtered and then concentrated under reduced pressure. Purification by chromatography (silica, 95:5 to 9:1 CH₂Cl₂/MeOH) gave a yellow oil. The oil was dissolved in 3:1 EtOAc/hexanes and then acidified with 1N HCl/Et₂O to give alkene **79** (7.15 g, 70%) as a white solid:
- ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.44 (s, 1H), 7.07 (dd, *J* 8, 8 Hz, 2H), 6.96 (dd, *J* 8, 8 Hz, 2H), 6.89 (s, 1H), 6.84 (s, 1H), 4.25 (q, *J* 7 Hz, 2H), 3.87 (d, *J* 5 Hz, 2H), 3.47 (br. d, *J* 12 Hz, 2H), 2.66-2.62 (m, 2H), 2.60 (d, *J* 7 Hz, 2H), 2.11-2.03 (m, 2H), 1.79 (br. d, *J* 14 Hz, 2H), 1.69-1.63 (m, 1H), 1.31 (t, *J* 7 Hz, 3H).
- Step 2:** Coupling of **70** (600 mg, 2.82 mmol) and alkene **79** (875 mg, 2.56 mmol) following the procedure described in Example 17, Step 5, gave the ester as an impure solid. The crude ester was saponified with excess LiOH in 1:1 MeOH/THF (15 mL). After stirring overnight, the reaction solvent was removed under reduced pressure. Purification by chromatography (silica, 89:10:1 to 79:20:1 CH₂Cl₂/MeOH/AcOH) followed by trituration with MeOH gave 5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (275 mg, 85%) as a white solid: mp 188-194°C

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IR (KBr): 2959, 2921, 1774, 1630, 1509 cm^{-1}

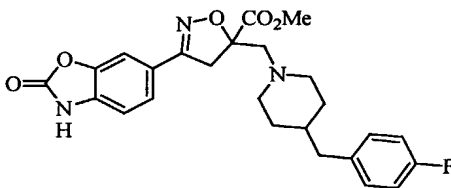
^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 11.92 (s, 1H), 7.58 (s, 1H), 7.48 (d, J 8 Hz, 1H), 7.24-7.07 (m, 8H), 3.89 (d, J 17 Hz, 1H), 3.45-3.16 (m, 5H), 2.60-2.50 (m, 2H), 1.64 (m, 3H), 1.31 (m, 2H)

5 ESI-MS (m/z): 454 $[\text{M} + \text{H}]^+$

HPLC: method C, 6.56 min (97.0%); method D, 12.33 min (99.5%); Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_3\text{O}_5 \cdot 0.5\text{H}_2\text{O}$: C, 62.33; H, 5.45; N, 9.09. Found: C, 62.57; H, 5.47; N, 9.00.

EXAMPLE 23

- 10 5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid methyl ester



- To a solution of 5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid (687 mg, 0.909 mmol) in MeOH (20 mL) and TFA (1.5 mL) was added *p*-toluenesulfonic acid monohydrate (190 mg, 0.999 mmol). The reaction mixture was heated to reflux overnight, then concentrated and purified by flash chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give 5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (133 mg, 31%), as an off white solid: mp 146-155°C

IR (KBr): 2930, 1767, 1508, 1448 cm^{-1}

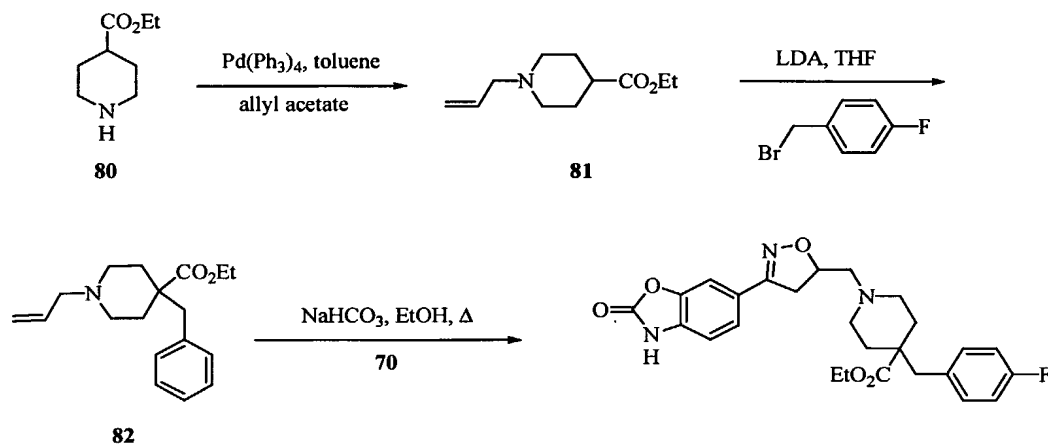
- ^1H NMR (500 MHz, CD_3OD): δ 7.58 (d, J 1 Hz, 1H), 7.51 (dd, J 8, 1 Hz, 1H), 7.20 (dd, J 8, 5 Hz, 2H), 7.16 (d, J 8 Hz, 1H), 7.03 (d, J 9 Hz, 1H), 7.00 (d, J 9 Hz, 1H), 3.96 (d, J 18 Hz, 1H), 3.92-3.90 (m, 4H), 3.68 (d, J 18 Hz, 1H), 3.68-3.55 (m, 3H), 3.21-3.05 (m, 2H), 2.62 (d, J 7 Hz, 2H), 1.97-1.83 (m, 3H), 1.71-1.55 (m, 2H)

APCI (m/z): 468 $[M + H]^+$

HPLC: method A, 6.32 min, 98.7%; Anal. Calcd for $C_{24}H_{26}FN_3O_5 \cdot HCl$: C, 59.58; H, 5.40; N, 8.34. Found: C, 59.19; H, 5.56; N, 8.01.

EXAMPLE 24

- 5 4-(4-Fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid ethyl ester



- Step 1:** Treatment of amine **80** (2.0 g, 13 mmol) with allyl acetate (1.6 mL, 14 mmol), and $Pd(Ph_3)_4$ (440 mg, 3.8 mmol), following the procedure described
10 in Example 20, Step 1, gave **81** (2.3 g, 88%):

1H NMR (300 MHz, $CDCl_3$): δ 5.97-5.79 (m, 1H), 5.26-5.10 (m, 2H), 4.21-4.09 (m, 2H), 2.99-2.87 (m, 4H), 2.35-2.20 (m, 1H), 2.04-1.65 (m, 6H), 1.27-1.22 (m, 3H).

- Step 2:** To an ice-cold solution of diisopropylamine (0.78 mL, 5.6 mmol) in THF
15 (22 mL) was added n -BuLi (2.2 mL of a 2.5 M solution in hexanes, 5.6 mmol). After 15 minutes, the reaction mixture was cooled in a $-78^\circ C$ dry ice/2-PrOH bath and then a solution of **81** (1.0 g, 5.1 mmol) in THF (10 mL) was added dropwise over 15 minutes. After 1.5 hours, a solution of 4-fluorobenzyl bromide (0.66 mL, 5.3 mmol) in THF (10 mL) was added dropwise to the reaction mixture over
20 1.5 hours. The reaction mixture was stirred for an additional 35 minutes and then warmed to ambient temperature. The reaction mixture was poured into H_2O and extracted with EtOAc (3 \times). The combined organics were dried (Na_2SO_4) and

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concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4.5:0.5 CH₂Cl₂/MeOH/NH₄OH) gave **82** (1.3 g, 81%):

¹H NMR (300 MHz, CDCl₃) δ 7.03-6.90 (m, 4H), 5.90-5.79 (m, 1H), 5.18-5.11 (m, 2H), 4.09 (q, *J* 7 Hz, 2H), 2.94 (d, *J* 7 Hz, 2H), 2.78 (s, 4H), 2.13 (d, *J* 13 Hz, 2H), 1.96 (dd, *J* 12, 12 Hz, 2H), 1.61-1.51 (m, 2H), 1.19 (t, *J* 7 Hz, 3H).

Step 3: Coupling of **70** (1.0 g, 4.7 mmol) and alkene **82** (1.3 g, 4.2 mmol) following the procedure described in Example 17, Step 5, gave 4-(4-fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid ethyl ester (630 mg, 31%), as a white solid: mp 212-214°C

IR (KBr): 2836, 1767, 1705, 1511, 1451 cm⁻¹

¹H NMR (300 MHz, DMSO-*d*₆): δ 11.80 (br s, 1H), 7.55 (d, *J* 1 Hz, 1H), 7.45 (dd, *J* 8, 1 Hz, 1H), 7.14 (d, *J* 8 Hz, 1H), 7.08 (d, *J* 8 Hz, 4H), 4.83-4.77 (m, 1H), 4.04 (dd, *J* 14, 7 Hz, 2H), 3.44 (dd, *J* 17, 7 Hz, 1H), 3.12 (dd, *J* 17, 7 Hz, 1H), 2.84-2.76 (m, 4H), 2.52-2.43 (m, 2H), 2.08-2.00 (m, 2H), 1.94-1.91 (m, 2H), 1.53-1.47 (m, 2H), 1.14 (dd, *J* 7, 7 Hz, 3H)

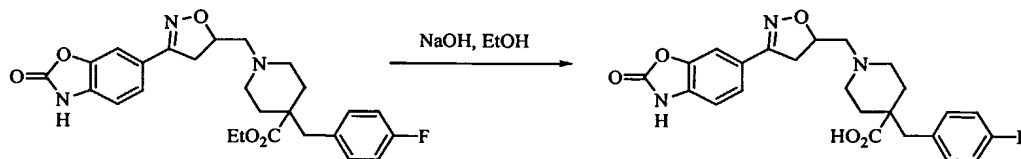
APCI (*m/z*): 482 [M + H]⁺

HPLC: method B, 11.50 min (97.5%); Anal. Calcd for C₂₆H₂₈FN₃O₅: C, 64.85; H, 5.86; N, 8.73. Found: C, 64.56; H, 5.74; N, 8.62.

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EXAMPLE 25

4-(4-Fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid



Step 1: A mixture of 4-(4-fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid ethyl ester (390 mg, 0.81 mmol) and 20% aq. NaOH (4.5 mL) in EtOH (4.5 mL) was heated to reflux for 16 hours. After stirring at ambient temperature overnight, the reaction

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solvent was removed under reduced pressure. The reaction mixture was diluted with water, brought to pH 3 with 1N HCl, and extracted with EtOAc (2×). The combined extracts were dried (Na₂SO₄) and concentrated under reduced pressure. Purification by chromatography (silica, 79:20:1 CH₂Cl₂/MeOH/AcOH) followed by recrystallization from MeOH/Et₂O gave 4-(4-fluorobenzyl)-1-[3-(2-oxo-2,3-

5 dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid (28 mg, 8%) as a yellow solid:

IR (KBr): 2922, 1767, 1600, 1508, 1448 cm⁻¹

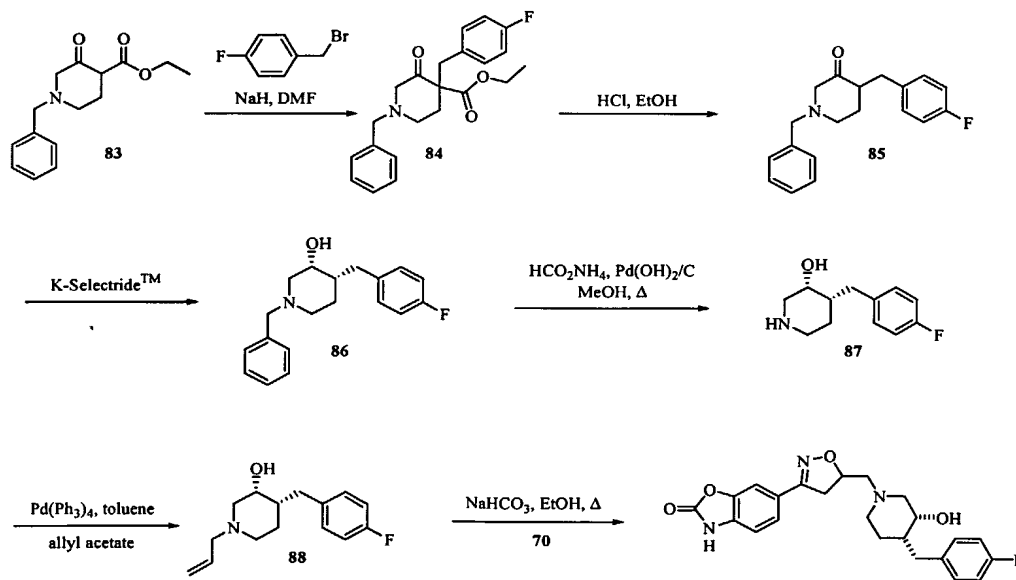
¹H NMR (500 MHz, DMSO-*d*₆): δ 7.55 (d, *J* 1 Hz, 1H), 7.45 (dd, *J* 8, 2 Hz, 1H),
 10 7.14-7.11 (m, 3H), 7.07 (d, *J* 8, 8 Hz, 2H), 3.46-3.10 (m, 4H), 2.79-2.73 (m, 4H),
 2.52-2.43 (m, 2H), 2.13-2.06 (m, 2H), 1.89-1.87 (m, 2H), 1.47-1.42 (m, 2H)

ESI-MS (*m/z*): 454 [M + H]⁺

HPLC: method A, 5.30 min (>99%).

EXAMPLE 26

15 6-{5-[4-(4-Fluorobenzyl)-3-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one



Step 1: To an ice-cold suspension of NaH (2.6 g, 110 mmol) in DMF (130 mL) was added 83 (15.0 g, 50 mmol) portionwise so that the internal reaction

20 temperature was maintained between 5°C to 10°C. After stirring at ambient

temperature for 1 hour, the reaction mixture was cooled in an ice/H₂O bath and a solution of 4-fluorobenzyl bromide (9.4 g, 50 mmol) in DMF (26 mL) was added. After stirring at ambient temperature for 15 hours, the reaction mixture was cooled in an ice/H₂O bath, and quenched by the addition of sat. NaHCO₃. The mixture

5 was diluted with H₂O (200 mL) and extracted with EtOAc (3 × 200 mL). The combined extracts were washed with H₂O (100 mL) and sat. NaCl (100 mL), dried (MgSO₄), and concentrated under reduced pressure. Purification by flash chromatography (silica, 8:1 hexanes/EtOAc followed by 4:1 hexanes/EtOAc) gave 84 (9.0 g, 49%):

10 ¹H NMR (300 MHz, CDCl₃): δ 7.35-7.19 (m, 5H), 7.11 (dd, *J* 8, 3 Hz, 2H), 6.92 (dd, *J* 8, 8 Hz, 2H), 4.16-3.99 (m, 2H), 3.51 (q, *J* 13 Hz, 2H), 3.28-2.84 (m, 4H), 2.78-2.61 (m, 1H), 2.61-2.48 (m, 2H), 1.68-1.58 (m, 1H), 1.09 (t, *J* 7 Hz, 3H).

Step 2: To a solution of 84 (8.9 g, 24 mmol) in EtOH (13 mL) was added conc.

HCl (30 mL), and the solution was heated to reflux. After 21 hours, the reaction

15 mixture was cooled in an ice/H₂O bath, brought to pH 8 with 1N NaOH and then extracted with EtOAc (3 × 200 mL). The combined extracts were washed with H₂O (100 mL) and sat. NaCl (100 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give 85 (6.5 g, 89%), which was used without further purification:

20 ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 7.11 (dd, *J* 8, 3 Hz, 2H), 6.95 (dd, *J* 8, 8 Hz, 2H), 3.57 (s, 2H), 3.26 (d, *J* 12 Hz, 2H), 2.94-2.79 (m, 2H), 2.47-2.34 (m, 3H), 1.93-1.87 (m, 1H), 1.71-1.52 (m, 1H).

Step 3: To a cold (-78°C dry ice/2-PrOH bath) solution of 85 (8.8 g, 29 mmol) in THF (200 mL) was added K-selectride™ (44 mL of a 1 M solution in THF,

25 44 mmol) at a rate that maintained the internal reaction temperature below -65°C. After the addition was complete, the reaction mixture was stirred for 1 hour (internal temperature -65°C) and then warmed to ambient temperature. The reaction was quenched by the addition of sat. NaHCO₃ (100 mL) and then extracted with EtOAc (2 × 200 mL). The combined extracts were washed with

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H₂O (100 mL) and sat. NaCl (100 mL), dried (Na₂SO₄), and concentrated under reduced pressure. Purification by flash chromatography (silica, 2:1 hexanes/EtOAc followed by 1:2 hexanes/EtOAc) gave 86 (4.0 g, 46%):

¹H NMR (300 MHz, CDCl₃): δ 7.33-7.25 (m, 5H), 7.15 (dd, *J* 6, 3 Hz, 2H), 6.95 (dd, *J* 8, 8 Hz, 2H), 3.57-3.52 (m, 1H), 3.50 (s, 2H), 2.96-2.71 (m, 3H), 2.58-2.49 (m, 1H), 2.07 (d, *J* 12 Hz, 1H), 2.09-1.92 (m, 1H), 1.62-1.30 (m, 4H).

Step 4: A mixture of compound 86 (4.0 g, 13 mmol), ammonium formate (1.7, 27 mmol), and 20% Pd(OH)₂/C (500 mg) in MeOH (50 mL) was heated at reflux for 1.5 hours. The reaction mixture was cooled to ambient temperature, filtered through Celite, and the filtrate was concentrated under reduced pressure to give amine 87 (2.8 g, 100%), which was used without further purification:

¹H NMR (300 MHz, CDCl₃): δ 7.15 (dd, *J* 6, 3 Hz, 2H), 6.96 (dd, *J* 8, 8 Hz, 2H), 3.55 (br. s, 1H), 3.48 (s, 2H), 3.03 (dd, *J* 12, 12 Hz, 2H), 2.75-2.48 (m, 4H), 1.68-1.31 (m, 3H).

Step 5: Treatment of amine 87 (1.4 g, 6.6 mmol) with allyl acetate (0.79 mL, 7.3 mmol), and Pd(Ph₃)₄ (380 mg, 0.30 mmol), following the procedure described in Example 20, Step 1, gave 88 (1.1 g, 66%):

¹H NMR (300 MHz, CDCl₃): δ 7.14 (dd, *J* 8, 3 Hz, 2H), 6.96 (dd, *J* 8, 8 Hz, 2H), 5.90-5.76 (m, 1H), 5.18-5.11 (m, 2H), 3.58-3.56 (m, 1H), 3.00-2.48 (m, 6H), 2.05-1.81 (m, 2H), 1.61-1.31 (m, 4H).

Step 6: Coupling of 70 (500 mg, 2.4 mmol) and alkene 88 (530 mg, 2.1 mmol) following the procedure described in Example 17, Step 5, followed by conversion to the HCl salt, gave 6-{5-[4-(4-fluorobenzyl)-3-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (288 mg, 29%), as a white solid: mp 224-233°C

IR (KBr): 2957, 1771, 1509, 1453 cm⁻¹

¹H NMR (300 MHz, CD₃OD): δ 7.58-7.57 (m, 1H), 7.53-7.49 (m, 1H), 7.27-7.23 (m, 2H), 7.16-7.12 (m, 1H), 7.05-6.99 (m, 2H), 5.28-5.07 (m, 1H), 3.89 (br s, 1H), 3.76-3.62 (m, 1H), 3.48-3.01 (m, 6H), 2.82-2.59 (m, 2H), 2.11-1.85 (m, 2H), 1.75-1.62 (m, 2H)

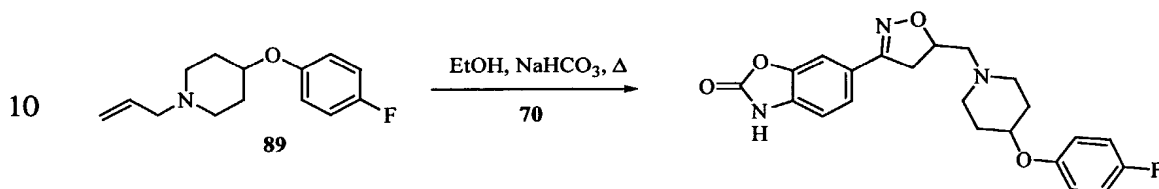
APCI (m/z): 426 $[M + H]^+$

HRMS-API (m/z): $[M + H]^+$ Calcd for $C_{23}H_{24}FN_3O_4$, 426.1829; Found, 426.1834

HPLC: method A, 6.15 min (96.1%); method B, 11.07 min (>99%); Anal. Calcd for $C_{23}H_{24}FN_3O_4 \cdot HCl \cdot 0.25H_2O$: C, 59.23; H, 5.51; N, 9.01. Found: C, 59.16; H, 5.41; N, 8.87.

EXAMPLE 27

6-{5-[4-(4-Fluorophenoxy)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3H-benzoxazol-2-one



Step 1: A mixture of 4-(4-fluorophenoxy)piperidine hydrochloride (1.48 g, 6.40 mmol) and $NaHCO_3$ (1.34 g, 16.0 mmol) in DMF (30 mL) was heated to 50°C for 30 minutes. Allyl bromide (0.550 mL, 6.40 mmol) was added and the reaction mixture was stirred at 50°C for 2 hours. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (1×). The combined organic extracts were washed with sat. NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5 to 9:1 CH_2Cl_2 /MeOH) gave 89 (621 mg, 41%) as an oil:

20 1H NMR (300 MHz, $CDCl_3$): δ 6.96 (dd, J 9, 9 Hz, 2H), 6.88-6.83 (m, 2H), 5.95-5.82 (m, 1H), 5.22-5.13 (m, 2H), 4.26-4.19 (m, 1H), 3.03 (d, J 7 Hz, 2H), 2.74-2.72 (m, 2H), 2.32-2.25 (m, 2H), 2.02-1.95 (m, 2H), 1.86-1.75 (m, 2H).

Step 2: To a mixture of alkene 89 (620 mg, 2.63 mmol) and $NaHCO_3$ (400 mg, 4.76 mmol) in 2:1 DMF/ H_2O (3 mL) was added a solution of 70 (500 mg,

25 2.35 mmol) in DMF (2 mL). The mixture was heated to 50°C for 2 hours. The reaction mixture was partitioned between EtOAc and water. The aqueous layer

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was extracted with EtOAc (2×). The combined organic extracts were washed with sat. NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH₂Cl₂/MeOH/NH₄OH) and (silica, 1:1 hexanes/EtOAc to EtOAc to 89:10:1 CH₂Cl₂/MeOH/NH₄OH) followed by

5 crystallization from MeOH gave 6-{5-[4-(4-fluorophenoxy)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (225 mg, 19%):

mp 192-194°C

IR (KBr): 2951, 1779 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆): δ 11.78 (s, 1H), 7.55 (d, *J* 1 Hz, 1H), 7.45 (dd, *J* 8, 1 Hz, 1H), 7.13 (d, *J* 8 Hz, 1H), 7.07 (dd, *J* 9, 9 Hz, 2H), 6.94 (dd, *J* 9, 4 Hz, 2H), 4.86-4.80 (m, 1H), 4.31-4.26 (m, 1H), 3.46 (dd, *J* 17, 11 Hz, 1H), 3.16 (dd, *J* 17, 8 Hz, 1H), 2.81-2.75 (m, 2H), 2.60-2.51 (m, 2H), 2.38-2.30 (m, 2H), 1.91-1.88 (m, 2H), 1.63-1.56 (m, 2H)

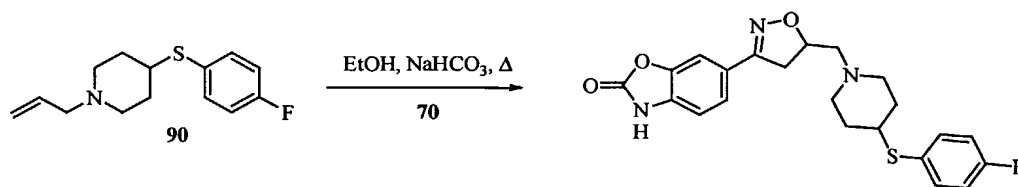
APCI-MS (*m/z*): 412 [M + H]⁺

15 HPLC: method A, 6.23 min (>99%)

Anal. Calcd for C₂₂H₂₂FN₃O₄: C, 64.22; H, 5.39; N, 10.21. Found: C, 64.00; H, 5.46; N, 10.08.

EXAMPLE 28

6-{5-[4-(4-Fluorophenylsulfanyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-
20 3*H*-benzoxazol-2-one



Step 1: Coupling of 4-(4-fluorophenylsulfanyl)piperidine hydrochloride (647 mg, 2.61 mmol) with allyl bromide (250 μL, 2.87 mmol) following the procedure described in Example 16, Step 1, gave alkene 90 (271 mg, 40%):

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^1H NMR (500 MHz, CD_3OD): δ 7.46 (dd, J 9, 5 Hz, 2H), 7.05 (dd, J 9, 9 Hz, 2H), 5.89-5.80 (m, 1H), 5.21-5.15 (m, 2H), 3.08-3.02 (m, 1H), 3.00 (d, J 7 Hz, 2H), 2.90-2.87 (m, 2H), 2.13-2.08 (m, 2H), 1.95-1.91 (m, 2H), 1.63-1.56 (m, 2H).

Step 2: Coupling of **70** (252 mg, 1.18 mmol) and alkene **90** (271 mg, 1.08 mmol)

5 following the procedure described in Example 17, Step 5, gave 6-{5-[4-(4-fluorophenyl)sulfanyl]piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (370 mg, 80%):

mp 190-192°C

IR (KBr): 2945, 1774 cm^{-1}

10 ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 11.80 (s, 1H), 7.54 (d, J 1 Hz, 1H), 7.47-7.43 (m, 3H), 7.18 (dd, J 9, 9 Hz, 1H), 7.13 (d, J 8 Hz, 1H), 4.84-4.78 (m, 1H), 3.44 (dd, J 17, 11 Hz, 1H), 3.18-3.09 (m, 2H), 2.90-2.83 (m, 2H), 2.56-2.48 (m, 2H), 2.21-2.14 (m, 2H), 1.85-1.83 (m, 2H), 1.51-1.42 (m, 2H)

ESI-MS (m/z): 428 $[\text{M} + \text{H}]^+$

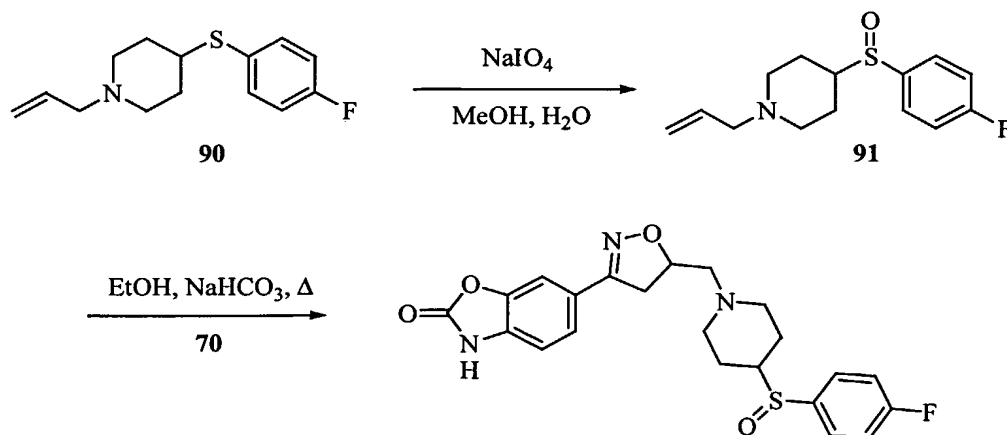
15 HPLC: method A, 6.40 min (98.9%); method B, 11.50 min (99.0%)

Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{FN}_3\text{O}_3\text{S}$: C, 61.81; H, 5.19; N, 9.83. Found: C, 62.13; H, 5.05; N, 9.86.

EXAMPLE 29

6-{5-[4-(4-Fluorobenzenesulfinyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one

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Step 1: To a solution of 90 (0.80 g, 3.18 mmol) in MeOH (10 mL) and H₂O (1.5 mL) was added NaIO₄ (680 mg, 3.18 mmol) at ambient temperature. The reaction mixture was stirred for 12 hours, and then additional NaIO₄ (100 mg, 0.47 mmol) was added. After 12 hours, the reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography (silica, 9:1 to 8:2 CH₂Cl₂/MeOH) gave 91 (240 mg, 28%) as a yellow wax:

¹H NMR (300 MHz, CDCl₃): δ 7.69-7.57 (m, 2H), 7.33-7.16 (m, 2H), 5.82 (dddd, *J* 17, 13, 10, 7 Hz, 1H), 5.22-5.12 (m, 2H), 3.10-2.93 (m, 4H), 2.65-2.52 (m, 1H), 2.03-1.88 (m, 2H), 1.81-1.52 (m, 4H).

Step 2: Coupling of 70 (209 mg, 0.98 mmol) and alkene 91 (230 mg, 0.86 mmol) following the procedure described in Example 17, Step 5, followed by conversion to the HCl salt, gave 6-{5-[4-(4-fluorobenzenesulfinyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (290 mg, 76%):

mp 170-178°C

IR (KBr): 2954, 1764 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆): δ 11.92 (s, 1H), 10.23 (br s, 1H), 7.73 (d, *J* 6 Hz, 1H), 7.71 (d, *J* 5 Hz, 1H), 7.56 (s, 1H), 7.52-7.44 (m, 3H), 7.15 (d, *J* 8 Hz, 1H), 5.22 (br s, 1H), 3.72 (m, 3H), 3.40-3.25 (m, 3H), 3.12 (m, 3H), 2.12 (br s, 1H), 2.01-1.75 (m, 2H), 1.67 (br s, 1H); APCI-MS (*m/z*): 444 [M + H]⁺

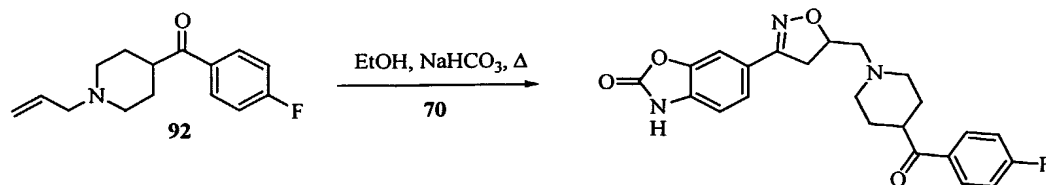
HPLC: method A, 4.61 min (95.0%); method B, 8.76 min (93.8%)

Anal. Calcd for C₂₂H₂₂FN₃O₄S·HCl·0.5H₂O: C, 54.04; H, 4.95; N, 8.59. Found: C, 54.06; H, 4.73; N, 8.38.

EXAMPLE 30

6-{5-[4-(4-Fluorobenzoyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one

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Step 1: Coupling of (4-fluorophenyl)piperidin-4-yl-methanone (1.50 g,

6.62 mmol) with allyl bromide (630 μ L, 7.28 mmol) following the procedure described in Example 16, Step 1 gave alkene 92 (830 mg, 51%):

5 ^1H NMR (300 MHz, CDCl_3): δ 7.97 (dd, J 8, 6 Hz, 2H), 7.14 (dd, J 9, 8 Hz, 2H), 5.94-5.85 (m, 1H), 5.23-5.14 (m, 2H), 3.22-3.17 (m, 1H), 3.04-3.00 (m, 4H), 2.13-2.05 (m, 2H), 1.92-1.80 (m, 4H)

Step 2: Coupling of 708 (787 mg, 3.70 mmol) and alkene 92 (830 mg, 3.36 mmol) following the procedure described in Example 17, Step 5 gave 6-{5-[4-(4-

10 fluorobenzoyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (465 mg, 33%):

mp 188-190°C; IR (KBr): 2950, 1776 cm^{-1}

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 11.76 (s, 1H), 8.05 (dd, J 9, 5 Hz, 2H), 7.56 (s, 1H), 7.47 (dd, J 9, 2 Hz, 1H), 7.34 (t, J 9 Hz, 2H), 7.14 (d, J 9 Hz, 1H),
15 4.92-4.80 (m, 1H), 3.48-3.09 (dd, J 17, 10 Hz, 1H), 3.39 (m, 1H), 3.18 (dd, J 17, 8 Hz, 1H), 2.99 (m, 2H), 2.70-2.50 (m, 2H), 2.37-2.18 (m, 2H), 1.80-1.70 (m, 2H), 1.65-1.54 (m, 2H)

ESI-MS (m/z): 424 $[\text{M} + \text{H}]^+$

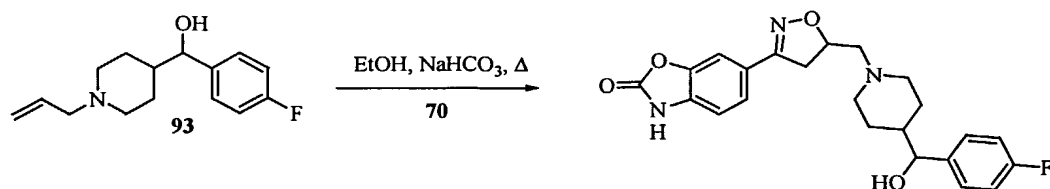
HPLC: method A, 5.81 min (95.1%); method B, 10.92 min (97.1%)

20 Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{FN}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$: C, 64.55; H, 5.30; N, 9.82. Found: C, 64.64; H, 5.04; N, 9.75.

EXAMPLE 31

6-(5-{4-[(4-Fluorophenyl)hydroxymethyl]piperidin-1-ylmethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one

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Step 1: To an ice-cold solution of alkene 92 (507 mg, 2.05 mmol) in 1:1 MeOH/CH₂Cl₂ (10 mL) was added NaBH₄ (67.3 mg, 2.41 mmol) portionwise.

The reaction was quenched with sat. NH₄Cl (1 mL) and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The organic layer was washed with sat. NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH₂Cl₂/MeOH/NH₄OH) gave alkene 93 (252 mg, 49%) as an off-white solid:

¹H NMR (300 MHz, CDCl₃): δ 7.29-7.25 (m, 3H), 7.05-7.00 (m, 2H), 5.92-5.78 (m, 1H), 5.18-5.10 (m, 2H), 4.37 (d, *J* 7 Hz, 1H), 3.01-2.85 (m, 4H), 2.00-1.21 (m, 7H).

Step 2: Coupling of 70 (738 mg, 3.48 mmol) and alkene 93 (722 mg, 2.90 mmol) following the procedure described in Example 17, Step 5, followed by conversion to the HCl salt gave 6-(5-{4-[(4-fluorophenyl)hydroxymethyl]piperidin-1-ylmethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one (951 mg, 81%): mp 186-191°C

IR (KBr): 3393, 2958, 1771 cm⁻¹

¹H NMR (300 MHz, CD₃OD): δ 7.58 (s, 1H), 7.51 (d, *J* 8 Hz, 1H), 7.37 (dd, *J* 8, 5 Hz, 2H), 7.15-7.39 (m, 3H), 5.26-5.13 (m, 1H), 4.46 (d, *J* 7 Hz, 1H), 4.04-3.62 (m, 3H), 3.42-3.19 (m, 4H), 3.12-2.97 (m, 2H), 2.19-2.10 (m, 1H), 1.98-1.82 (m, 1H), 1.80-1.55 (m, 3H)

APCI-MS (*m/z*): 426 [M + H]⁺

HPLC: method A, 5.51 min (>99%); method B, 10.40 min (97.9%)

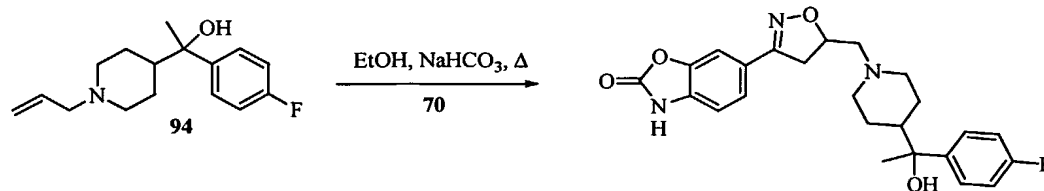
Anal. Calcd for C₂₃H₂₄FN₃O₄·HCl·0.25H₂O: C, 59.23; H, 5.51; N, 9.01. Found:

C, 59.11; H, 5.29; N, 8.75.

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EXAMPLE 32

6-(5-{4-[1-(4-Fluorophenyl)-1-hydroxyethyl]piperidin-1-ylmethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one



Step 1: To an ice-cold solution of MeMgBr (1.15 mL of a 3.0 M solution in Et₂O, 3.46 mmol) was added dropwise a solution of ketone 92 (712 mg, 2.88 mmol) in dry Et₂O. After 1 hour, the reaction was quenched with MeOH (1 mL) and sat. NH₄Cl (1 mL). The mixture was partitioned between water and Et₂O. The aqueous layer was extracted with Et₂O. The combined organic layers were washed with sat. NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 CH₂Cl₂/MeOH) gave alkene 94 as a yellow oil (755 mg, 92%):

¹H NMR (300 MHz, CDCl₃): δ 7.39-7.34 (m, 2H), 7.03-6.97 (m, 2H), 5.93-5.79 (m, 1H), 5.18-5.12 (m, 2H), 2.96 (d, *J* 6 Hz, 4H), 1.89-1.81 (m, 3H), 1.63-1.48 (m, 5H), 1.44-1.26 (m, 3H).

Step 2: Coupling of 70 (755 mg, 3.56 mmol) and alkene 94 (693 mg, 3.23 mmol) following the procedure described in Example 17, Step 5 gave 6-(5-{4-[1-(4-fluorophenyl)-1-hydroxyethyl]piperidin-1-ylmethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one (1.00 g, 64%):

mp 125-134°C

IR (KBr): 3427, 2944, 1774 cm⁻¹

¹H NMR (300 MHz, DMSO-*d*₆): δ 11.79 (s, 1H), 7.55 (s, 1H), 7.46-7.38 (m, 3H), 7.14-7.07 (m, 3H), 4.85-4.79 (m, 2H), 3.48-3.38 (m, 1H), 3.14-3.06 (m, 1H), 2.99-2.89 (m, 2H), 2.51-2.46 (m, 2H), 2.00-1.80 (m, 2H), 1.65-1.51 (m, 1H), 1.50-1.45 (m, 4H), 1.35-1.10 (m, 3H)

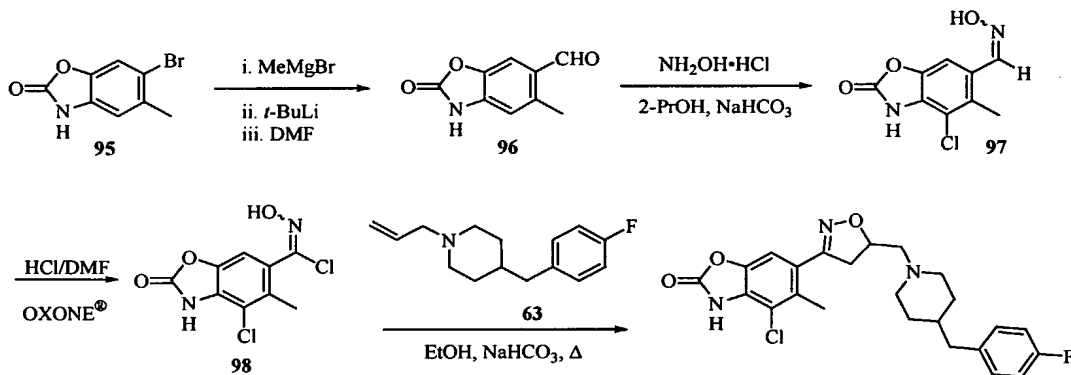
APCI-MS (*m/z*): 440 [M + H]⁺

HPLC: method A, 5.60 min (97.0%); method B, 10.70 min (98.2%)

Anal. Calcd for $C_{24}H_{26}FN_3O_4 \cdot 0.25H_2O$: C, 64.93; H, 6.02; N, 9.46. Found: C, 64.65; H, 5.85; N, 9.26.

EXAMPLE 33

4-Chloro-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-5-methyl-3H-benzoxazol-2-one



Step 1: To a -78°C solution of bromide **95** (10.3 g, 45.2 mmol) in THF (40 mL) was added MeMgBr (16.6 mL of a 3.0 M solution in diethyl ether, 49.7 mmol). After 40 minutes, anhydrous THF (410 mL) was added at a rate that maintained the internal reaction temperature below a threshold of -50°C . After the solution returned to -78°C , *tert*-butyl lithium (85 mL of a 1.7 M solution in pentane, 144 mmol) was added *via* a dropping funnel. After 10 minutes, DMF (21.0 mL, 271 mmol) was added to the yellow mixture, and then the cold bath was removed. After 2 hours, the reaction was quenched with water and the THF removed under reduced pressure. The residue was partitioned between EtOAc and 1N HCl. The aqueous layer was extracted with EtOAc (2 \times). The combined organic extracts were washed with sat. NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by crystallization from hot EtOH gave aldehyde **96** (2.86 g, 35%):

^1H NMR (300 MHz, CDCl_3): δ 11.60 (s, 1H), 10.23 (s, 1H), 7.58 (s, 1H), 6.91 (s, 1H), 2.68 (s, 3H).

Step 2: A mixture of aldehyde **96** (2.80 g, 15.8 mmol), hydroxylamine hydrochloride (1.21 g, 17.4 mmol), and sodium bicarbonate (1.99 g, 23.7 mmol) in

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2-PrOH (80 mL) was heated to 50°C for 4 hours. The warm mixture was diluted with MeOH, and filtered. Concentration under reduced pressure gave oxime 97 (3.69 g, 100%):

¹H NMR (300 MHz, DMSO-*d*₆): δ 11.17 (s, 1H), 8.30 (s, 1H), 7.41 (s, 1H), 6.91 (s, 1H), 2.36 (s, 3H).

Step 3: A mixture of oxime 97 (3.69 g, 15.8 mmol) and OXONE® (10.7 g, 17.4 mmol) was stirred in HCl (32.8 mL of a 0.53 M solution in DMF, 17.4 mmol) for 3 hours. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (2×). The combined organic
10 extracts were washed with water, sat. NaCl, dried (Na₂SO₄), and concentrated under reduced pressure. The yellow solid was dissolved in hot EtOAc. Addition of hexane to the solution gave 98 (3.04 g, 73%) as an off-white solid:

¹H NMR (300 MHz, DMSO-*d*₆): δ 12.45 (s, 1H), 7.96 (s, 1H), 7.42 (s, 1H), 2.33 (s, 3H); ESI-MS (negative mode) (*m/z*): 224 [(M-H)-HCl]⁻.

Step 4: Coupling of 98 (1.82 g, 6.99 mmol) and alkene 63 (1.63 g, 6.99 mmol) following the procedure described in Example 11, Step 2, gave 4-chloro-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-5-methyl-3*H*-benzoxazol-2-one (1.0 g, 31%):

mp 131-132°C

20 IR (KBr): 2922, 1780 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆): δ 12.20 (s, 1H), 7.35 (s, 1H), 7.17 (dd, *J* 8, 6 Hz, 2H), 7.07 (dd, *J* 9, 8 Hz, 2H), 4.82-4.76 (m, 1 H), 3.48 (dd, *J* 17, 11 Hz, 1H), 3.18 (dd, *J* 17, 8 Hz 1H), 2.91 (m, 2H), 2.58-2.46 (m, 4H), 2.45 (s, 3H), 2.08-1.99 (m, 2H), 1.52-1.42 (m, 3H), 1.22-1.13 (m, 2H)

25 ESI-MS (*m/z*): 458 [M + H]⁺

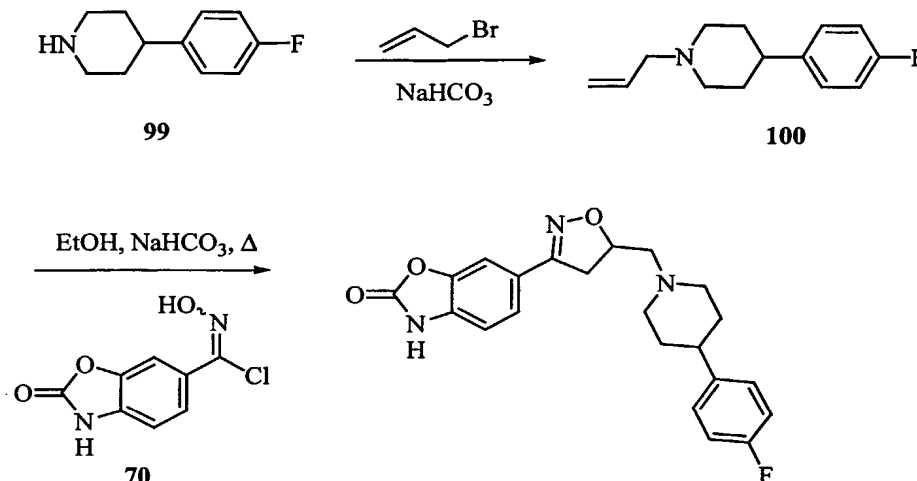
HPLC: method A, 6.95 min (96.0%); method B, 12.21 min (95.9%)

Anal. Calcd for C₂₄H₂₅ClFN₃O₃: C, 62.34; H, 5.56; N, 9.09. Found: C, 62.52; H, 5.44; N, 8.88.

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EXAMPLE 34

-{5-[4-(4-Fluorophenyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one



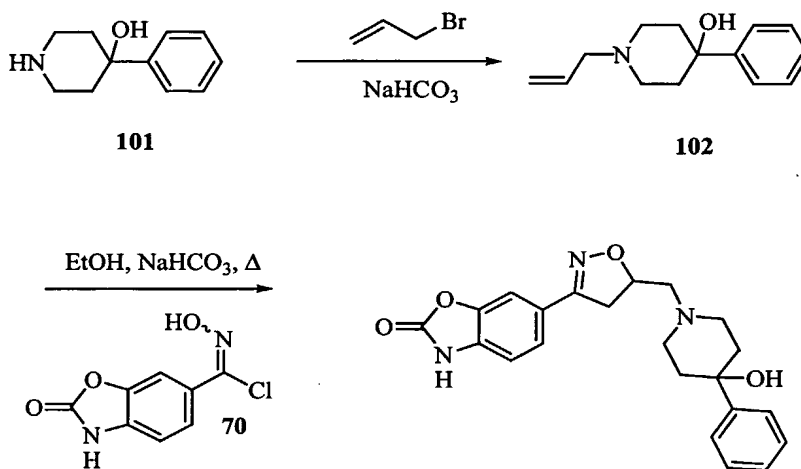
- 5 **Step 1:** Alkene of formula **100** was prepared following the procedure described below for alkene of formula **63** in Example 16, Step 1, to give 1.34 g, (50%):
- ^1H NMR (300 MHz, CDCl_3): δ 7.20-7.15 (m, 2H), 7.00-6.94 (m, 2H), 5.98-5.85 (m, 1H), 5.23 (d, J 16 Hz, 1H), 5.14 (d, J 10, 1H), 3.07-3.02 (m, 4H), 2.48 (dt, J 11, 5 Hz, 1H), 2.07-1.98 (m, 2H), 1.81-1.65 (m, 4H).
- 10 **Step 2:** Coupling of compound of formula **70** and alkene of formula **100** following the procedure described above in Example 17, Step 5, gave 6-{5-[4-(4-fluorophenyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one (719 mg, 70%):
- mp 214-217°C
- 15 IR (KBr): 2926, 1774 cm^{-1}
- ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 11.80 (s, 1H), 7.57 (d, J 1 Hz, 1H), 7.48 (dd, J 8, 1 Hz, 1H), 7.27 (dd, J 8, 6 Hz, 2H), 7.15 (d, J 8 Hz, 1H), 7.08 (dd, J 8, 6 Hz, 2H), 4.90-4.84 (m, 1H), 3.49 (dd, J 17, 11 Hz, 1H), 3.18 (dd, J 17, 8 Hz, 1H), 3.05 (d, J 11 Hz, 1H), 3.02 (d, J 11 Hz, 1H), 2.63-2.52 (m, 2H), 2.51-2.47 (m, 1H),
- 20 2.20-2.13 (m, 2H), 1.74-1.71 (m, 2H), 1.67-1.58 (m, 2H)
- ESI-MS (m/z): 396 $[\text{M} + \text{H}]^+$
- HPLC: method A, 4.83 minutes(98.3%); method B, 10.60 minutes(>99%)

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Anal. Calcd for $C_{22}H_{22}FN_3O_3 \cdot 0.25H_2O$: C, 66.07; H, 5.67; N, 10.51. Found: C, 66.13; H, 5.60; N, 10.52.

EXAMPLE 35

6-[5-(4-Phenyl-4-hydroxy)piperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3H-benzoxazol-2-one



Step 1: Alkene of formula **102** was prepared following the procedure described below for alkene of formula **63** in Example 16, Step 1, to give 1.24 g, (50%):

1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J 7 Hz, 2H), 7.36 (dd, J 7, 7 Hz, 1H), 7.28 (d, J 7 Hz, 2H), 6.00-5.86 (m, 1H), 5.25 (d, J 17 Hz, 1H), 5.16 (d, J 10 Hz, 1H), 3.10 (d, J 7 Hz, 2H), 2.86 (d, J 12 Hz, 2H), 2.45 (ddd, J 12, 12, 2 Hz, 2H), 1.31 (ddd, J 13, 13, 4 Hz, 2H), 1.79 (d, J 12 Hz, 2H), 1.63-1.55 (m, 1H).

Step 2: Coupling of compound of formula **70** and alkene of formula **102** following the procedure described above in Example 17, Step 5, gave 6-[5-(4-phenyl-4-hydroxy)piperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3H-benzoxazol-2-one (423 mg, 38%):

mp 115-118°C

IR (KBr): 2951, 1771 cm^{-1}

1H NMR (500 MHz, $DMSO-d_6$): δ 11.80 (s, 1H), 7.57 (s, 1H), 7.48-7.45 (m, 3H), 7.30 (dd, J 8, 8 Hz, 2H), 7.19 (dd, J 7, 6 Hz, 1H), 7.14 (d, J 8 Hz, 1H), 4.90-4.84 (m, 1H), 4.74 (s, 1H), 3.48 (dd, J 17, 11 Hz, 1H), 3.19 (dd, J 17, 8 Hz, 1H), 2.76-2.69 (m, 2H), 2.64-2.50 (m, 4H), 1.92 (dt, J 13, 4 Hz, 2H), 1.60-1.55 (m, 2H)

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ESI-MS (m/z): 394 $[M + H]^+$

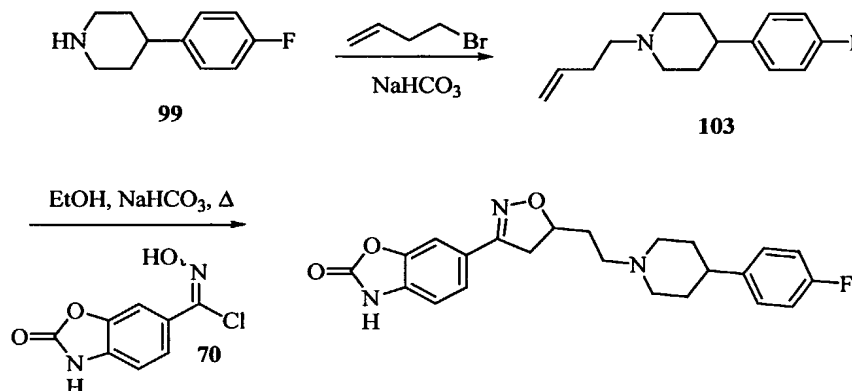
HPLC: method A, 5.48 min (>99%); method B, 9.63 min (>99%)

Anal. Calcd for $C_{22}H_{23}N_3O_4 \cdot 0.75H_2O$: C, 64.93; H, 6.07; N, 10.33. Found: C, 65.16; H, 6.03; N, 10.27.

5

EXAMPLE 36

6-(5-{2-[4-(4-Fluorophenyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one



Step 1: Alkene of formula **103** was prepared following the procedure described

below for alkene of formula **63** in Example 16, Step 1, to give 2.29 g, (85%):

1H NMR (300 MHz, $CDCl_3$): δ 7.22 (dd, J 9, 8 Hz, 2H), 6.99 (dd, J 9, 8 Hz, 2H), 5.85-5.72 (m, 1H), 5.14 (dd, J 18, 1 Hz, 1H), 5.12 (d, J 10 Hz, 1H), 3.48 (d, J 12 Hz, 2H), 2.88-2.83 (m, 2H), 2.71-2.59 (m, 5H), 2.36-2.31 (m, 2H), 1.97 (d, J 13 Hz, 2H).

Step 2: Coupling of compound of formula **70** and alkene of formula **103**

following the procedure described above in Example 17, Step 5, gave 6-(5-{2-[4-(4-fluorophenyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one (759 mg, 71%):

mp 188-194°C

IR (KBr): 3448, 2934, 1773, 1654 cm^{-1}

1H NMR (500 MHz, $DMSO-d_6$): δ 7.55 (d, J 1 Hz, 1H), 7.46 (dd, J 8, 1 Hz, 1H), 7.23 (dd, J 9, 8 Hz, 2H), 7.14 (d, J 8 Hz, 1H), 7.08 (dd, J 9, 8 Hz, 2H), 4.76-4.70 (m, 1H), 3.45 (dd, J 17, 11 Hz, 1H), 3.12 (dd, J 11, 8 Hz, 1H), 3.00 (d, J 12 Hz,

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1H), 2.95 (d, *J* 12 Hz, 1H), 2.49-2.36 (m, 4H), 2.04-1.98 (m, 2H), 1.86-1.48 (m, 6H)

ESI-MS (*m/z*): 410 [M + H]⁺

HPLC: method A, 5.58 min (98.8%); method B, 10.45 min (>99%)

- 5 Anal. Calcd for C₂₃H₂₄FN₃O₃·0.25H₂O: C, 66.73; H, 5.97; N, 10.15. Found: C, 66.81; H, 5.99; N, 9.91.

As noted above, the invention compounds are subtype selective NMDA receptor antagonists. The compounds have been evaluated in standard assays commonly used to measure activity. Typical assays were carried out as follows.

10

BIOLOGICAL METHODS

I. Electrophysiological assays at NMDA receptor subunits (*in vitro*):

a. The NR1A/NR2B assay:

(i) Preparation of subunit RNA's:

15 cDNA clones encoding the NR1A, NR2A, NR2B, and NR2C rat NMDA receptor subtypes were used. (See, Moriyoshi et al., *Nature (Lond.)*, 1991;354:31-37; Kutsuwada et al., *Nature (Lond.)*, 1992;358:36-41; Monyer et al., *Science* (Washington, D.C.) 1992;256:1217-1221; Ikeda et al., *FEBS Lett.* 1992;313: 34-38; Ishii et al., *J. Biol. Chem.*, 1993;268:2836-2843 for details of these clones or their mouse homologs). The clones were transformed into appropriate host bacteria and plasmid preparations were made with conventional DNA purification techniques. A sample of each clone was linearized by restriction enzyme digestion of cDNA was synthesized with T3 RNA polymerase. The cRNA was diluted to 400 ng/ μ l and stored in 1 μ l aliquots at -80°C until injection.

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(ii) The *Xenopus* oocyte expression system:

30 Mature female *Xenopus laevis* were anaesthetized (20 to 40 minutes) using 0.15% 3-aminobenzoic acid ethyl ester (MS-222) and 2 to 4 ovarian lobes were surgically removed. Oocytes at developmental stages IV-VI (Dumont, J.N., *J. Morphol.*, 1972;136:153-180) were dissected from the ovary still surrounded by enveloping ovarian

tissues. Follicle-enclosed oocytes were micro-injected with 1:1 mixtures of NR1A:NR2A, 2B or 2C; injecting 1 to 10 ng of RNA encoding each receptor subunit. NR1A encoding RNA was injected alone at ~20 ng. Oocytes were stored in Barth's medium containing (in mM) :NaCl, 88; KCl, 1; CaCl₂, 0.41; Ca (NO₃)₂, 0.33; MgSO₄, 0.82 NaHCO₃, 2.4; HEPES 5, pH 7.4, with 0.11 mg/mL gentamicin sulphate. While oocytes were still surrounded by enveloping ovarian tissues the Barth's medium was supplemented with 0.1% bovine serum. Oocytes were defolliculated 1 to 2 days following injections by treatment with collagenase (0.5 mg/mL Sigma Type I for 0.5 to 1 hour) (Miledi and Woodward, *J. Physiol. (Lond.)*, 1989;416:601-621) and subsequently stored in serum-free medium.

(iii) Electrical recordings:

Electrical recordings were made using a conventional two-electrode voltage clamp (Dagan TEV-200) over periods ranging between 3 to 21 days following injection. (Woodward et al., *Mol. Pharmacol.*, 1992;41:89-103). Oocytes were placed in a 0.1 mL recording chamber continuously perfused (5-15 mL min⁻¹) with frog Ringer's solution containing (in mM) :NaCl, 115; KCL, 2; BaCl₂, 1.8; HEPES, 5; pH 7.4. Drugs were applied by bath perfusion. Using oocytes expressing different subunit combinations of NMDA receptor, NMDA currents were activated by co-application of glutamate (100 μM) and glycine (1-100 μM) as agonists. Inhibitory potency of the novel antagonists of this invention was assessed on responses elicited by fixed concentrations of glutamate and glycine agonists, by measuring reductions in current induced by progressively increasing concentrations of invention compounds.

(iv) Concentration-inhibition curves:

Concentration-inhibition curves were fitted with equation 1

$$I/I_{\text{control}} = 1/(1 + ([\text{antagonist}]/10^{-\text{pIC}_{50}})^n) \text{ Eq. 1}$$

in which I_{control} is the current evoked by the agonists alone,
 $pIC_{50} = -\log IC_{50}$, IC_{50} is the concentration of invention compound
that produced half maximal inhibition of the electrical current, and n
is the slope factor (see De Lean et al., *Am. J. Physiol.*, 1978;235:
5 E97-102). For incomplete curves, analysis by fitting was unreliable,
and IC_{50} values were calculated by simple regression over linear
portions of the curves using an ORIGIN software (Microcal Software,
Boston, MA), a computer program for collection, analysis, and
presentation of scientific data. The results of this assay for
10 representative invention compounds is given in Table 1, in the column
labeled "NR1A/NR2B", and the activity is reported as the IC_{50} in
micromolar (μM) concentration.

b. [^3H]Ifenprodil Binding Assay (IFPNR) Protocol:

- (i) Materials:
- 15 Ifenprodil, [phenyl- ^3H]- (specific activity, 66.2 Ci/mmol) was
purchased from Dupont NEN Research Products (Boston, MA).
Ifenprodil tartrate was purchased from Research Biochemicals
International (Natick, MA). HEPES, glutamate and glycine were
purchased from Sigma Chemical Co. (St. Louis, MO).
- 20 (ii) Preparations:
- All buffers and reagents used in assay incubations or to dissolve
drugs were prepared using water purified through a Milli-Q reverse
osmosis system (Millipore Corp., Bedford, MA) and treated with UV
emissions. Prior to use in the assays buffers were further filtered
25 through a sterile Corning filtration unit (Corning Glass Works,
Corning, NY) containing a 0.2 micron filter. Buffer used to rinse the
membranes on the assay filters was prepared with purified water, but
was not refiltered and was stored no longer than 5 days. Stock
solutions of the drugs (usually 10 mM) were dissolved in 20 mM
30 HEPES-KOH buffer pH 7.4 (assay buffer) with the addition of 1 to
5 μL of glacial AcOH, if needed to keep them in solution. Eliprodil

was used as the reference NMDA antagonist. A stock solution of eliprodil was prepared, and was buffered with the addition of 10% DMSO. All subsequent dilutions from the stock solution were made in buffer.

5 An extensively washed buffy coat membrane fraction was prepared from frozen adult rat forebrains (Zivic-Miller Laboratories, Inc., Zelienople, PA) as described by Coughenour L.L.; Cordon, J.J., *J. Pharmacol. Exp. Ther.*, 1997;280:584-592, and stored at -80°C. On the day of the assay, pellets of the frozen membrane fractions
10 were resuspended in 35 mL of assay buffer at pH 7.4 using a POLYTRON (Kinematica A.G. Company, Littau, Switzerland) mixer at setting 6. After incubation at 37°C for 30 minutes in a shaking water bath, the homogenate was centrifuged $40,000 \times g$ for 10 minutes at 4°C. The pellets were resuspended in fresh buffer and
15 centrifuged 3 more times before final suspension for use in the assay.

(iii) [^3H]Ifenprodil Binding protocol:

Triplicate incubations were carried out in a volume of 0.5 mL in 1.3 mL polypropylene tubes (Marsh Biomedical Products Inc, Rochester, NY) for 2 hours at room temperature. Incubations
20 contained invention compounds, membranes (100-200 μg protein) and 4 nM [^3H]-ifenprodil in 20 mM HEPES-KOH buffer, pH 7.4 (assay buffer). Assays were started by addition of the membranes. Bound radioligand was separated by filtration under reduced pressure using a TOMTEC Mach II, 96-well cell harvester (Tomtec Inc,
25 Orange, Connecticut). Filtration was through Whatman GF/B glass fiber filters (Whatman Ltd., Maidstone, England), which had been soaked for at least 15 minutes in 0.3% polyethylenimine and allowed to air dry. The filters were rinsed with 3 mL of ice cold assay buffer within 6 seconds. Air was allowed to pass through the filters for an
30 additional 10 seconds to remove residual moisture. The filter mat was supported on a cold (-20°C) TEFLON (E. I. Du Pont de

Nemours and Company, Wilmington, Delaware) coated support, and filters from individual wells were separated and placed in Mini Poly-Q vials (Beckman Instruments Inc, Fullerton, CA) and filled with 4 mL of scintillation cocktail (Beckman Ready Protein⁺).

5 Radioactivity retained on the filter was determined by liquid scintillation spectrophotometry. Nonspecific binding was defined as the binding in the presence of 1 mM ifenprodil. Ninety percent of the total binding of ifenprodil was specific binding at the NR1A/NR2B NMDA receptor subtype active site (as opposed to binding at a remote site).

(iv) Data analysis:

Binding curves were statistically analyzed for a best 1- or 2-site competition fit using GRAPHPAD PRISM software (GraphPad Software Inc, San Diego, CA), a computer program used to analyze and graph scientific data. The normalized data was fitted by nonweighted nonlinear regression to either

$$y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{1 + 10^{x - \text{Log EC}_{50}}} \quad \text{or}$$

$$y = \text{Bottom} + (\text{Top} - \text{Bottom}) \frac{\text{Fraction-1}}{1 + 10^{x - \text{Log EC}_{50-1}}} + \frac{1 - \text{Fraction-1}}{1 + 10^{x - \text{Log EC}_{50-2}}}$$

Control data was entered as 100%, and no parameters were constrained. Inhibition curves were compared by Anova with post-test comparisons of the log IC₅₀ with Dunnett's multiple comparisons post-test or Student's nonpaired, 2-tailed t-test using GraphPad INSTAT (Harvey Motulsky, San Diego, CA) software.

The results of the IFPNR binding assay are reported as IC₅₀s in micromolar (μM) concentrations in Table 1 to Table 5 in the columns labeled "IFPNR".

II. Animal Models:

a. The Formalin Footpad Test (FT):

The FT model was used to test invention compounds for pain alleviating properties. The model produces a biphasic response in a test animal that results from a change in pain intensity over time. The FT model utilizes an injection of dilute formalin into the hindpaw of a rodent, which produces high intensity acute pain behaviors which are measured for the first 10 minutes post formalin injection (early phase responding). High intensity acute pain behaviors include rapid licking or biting of the injected hindpaw. The second phase is a prolonged period of lower intensity pain behaviors (late phase responding) which are measured from 11 to 45 minutes post-formalin injection.

(i) Test animals:

Male Wistar albino rats (Harlan Sprague-Dawley Labs), weighing approximately 100 g at the time of testing, were used. Animals were group-housed and acclimated to the housing facility for 1 week prior to testing. Animals were maintained on a 12-hour/12-hour light/dark cycle and fed block rodent chow. From 4 to 8 animals were randomly assigned to either a vehicle-only dose group or a vehicle-plus invention compound treatment group on the day of testing.

(ii) Test apparatus:

The testing apparatus was a 16" × 8" box divided into two 8" × 8" testing chambers. Each testing chamber comprised a floor and 3 walls made of clear plastic mirrors, and a fourth wall which was clear plastic that allowed observation of animal behavior. The top of each chamber was covered with a metal screen during testing to prevent animals from climbing out of the chamber. Two animals were tested simultaneously in the adjoining boxes, but animals were unable to observe one another.

(iii) Procedure:

Animals were weighed and placed into holding cages (2 animals per cage) in the testing room prior to dosing. Following approximately

30 minutes of acclimation to the testing room, each pair of animals was administered orally (PO) by gavage a mixture of invention compound plus vehicle or vehicle alone. The treated animals were then placed in individual test chambers and allowed to acclimate to the chambers for at least 20 minutes. Then 50 μ L of a 2.5% solution of formalin in vehicle was injected subcutaneously (SC) in the plantar surface of the left hindpaw from 30 to 120 minutes after administration of the invention compound. A session timer was started following the formalin injection, and the amount of time the animal spent licking or biting the injected paw was clocked with a hand-held stopwatch. The cumulative time spent engaging in a pain response was manually recorded at 5-minute intervals for 45 minutes post formalin injection. Early phase responding included Minutes 0 to 10, and late phase responding included Minutes 11 to 45. At the end of the testing period, animals were sacrificed using carbon dioxide.

(iv) Data Analysis:

As recited above, responding was divided into early phase (total time spent licking during Minutes 0 to 10 following the formalin injection) behaviors and late-phase (total time spent licking during Minutes 11 to 45 post formalin injection) behaviors. Time values were obtained for the vehicle only dose group (the control group) and each treatment group. For the purpose of measuring the activity of the invention compounds, the late-phase time values of a given treatment group were compared statistically to the late-phase time values obtained for the control group using either Student's t-test or One-way Analysis of Variants (ANOVA).

The results are reported in Table 1 and Table 2 under the heading "FT" as the dose tested in milligrams of invention compound per kilogram of test animal (mg/kg). A compound was characterized as active if it produced a statistically-significant decrease in the time animals administered invention compound plus vehicle spent

engaging in pain-related behaviors compared to the time spent by animals receiving vehicle alone. Invention compounds were typically administered at 10 and/or 30 mg/kg, and the activities are reported in the tables as either being greater than (>) or less than (<) these doses.

5 b. The 6-OHDA Lesioned Rat Assay (6-OHDA):

The 6-OHDA model is used to test compounds of the invention for anti-Parkinsonism activity.

(i) 6-OHDA lesioned rat assay protocol:

6-Hydroxydopamine-lesioned rats were used (see Ungerstedt U, Arbuthnott GW: "Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system", *Brain Res.*, 1971;24(3):485-493). Adult male Sprague-Dawley rats were anesthetized with chloral hydrate, and unilateral lesions of the nigrostriatal dopamine system were accomplished by infusion of 8 µg of 6-hydroxydopamine HBr (6-OHDA) into the right medial forebrain bundle. Rats were pretreated 30 minutes before surgery with desipramine HCl 25 mg/kg intraperitoneally (IP) to protect noradrenergic neurons, and pargyline 25 mg/kg IP to potentiate the effects of 6-OHDA. A minimum of 3 weeks after surgery, the rotational behavior induced by apomorphine HCl 50 µg/kg administered subcutaneously (SC) was assessed. Only rats demonstrating more than 100 contraversive turns/hour to apomorphine were used for the present experiments.

(ii) Measurement of animal behavior:

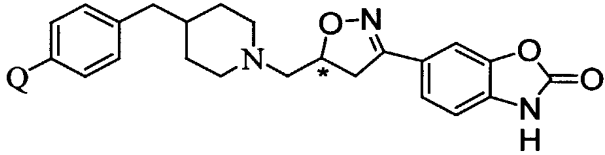
Rotational behavior was measured using an automatic rotometer system (Rotorat Rotational Activity System, MED Associates, Georgia, VT). Antiparkinsonian activity was assessed as the ability of the invention compounds to potentiate the contraversive rotation induced by L-DOPA methyl ester, dosed at 10 mg/kg SC, over a 6-hour period. Experiments were conducted using a crossover paradigm where each rat received either vehicle plus L-DOPA, or an invention compound plus L-DOPA, in randomized order. Rats were

tested at 7-day intervals. In experiments in which the invention compounds were tested orally (PO), rats were food deprived for 16 hours.

(iii) Data analysis:

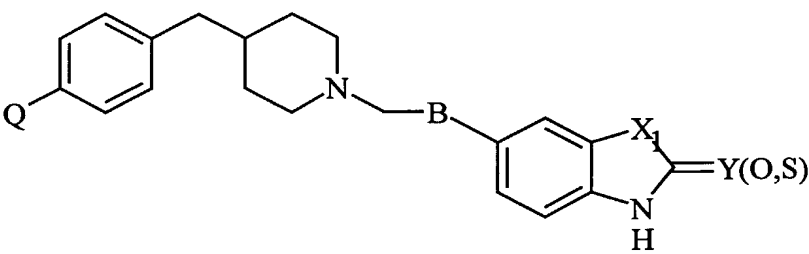
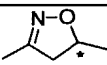
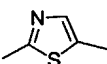
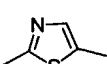
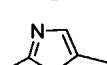
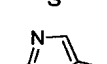
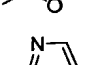
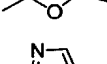
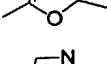
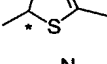
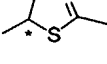
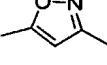
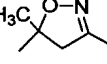
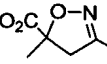
5 Statistical analysis between treatment groups was performed using a paired t-test. The results are reported in Table 1 and Table 2 under the heading "6-OHDA" as the minimum effective dose (MED) in milligrams of invention compound per kilogram of test animal (mg/kg) required to produce a statistically-significant increase in total
10 contraversive rotations in rats administered invention compound compared to rats receiving L-DOPA alone. Invention compounds were typically administered at 10 mg/kg and/or 30 mg/kg, and the MED's are reported in the tables as either being greater than (>) or less than (<) these doses.

TABLE 1

						
Example No.	Q	*	IFPNR (IC ₅₀ μM)	NR1A/ NR2B (IC ₅₀ μM)	6-OHDA (mg/kg)	FT (mg/kg)
1	H	<i>R,S</i>	0.033	0.080	>10 (po)	>10
3	F	<i>R,S</i>	0.030	NT ^a	>10 (po); <30 (po)	>10; <30
4a	F	(+)	0.016	NT	>10 (po); <30 (po)	<10
4b	F	(-)	0.280	NT	>30 (po)	>30

^a NT means not tested.

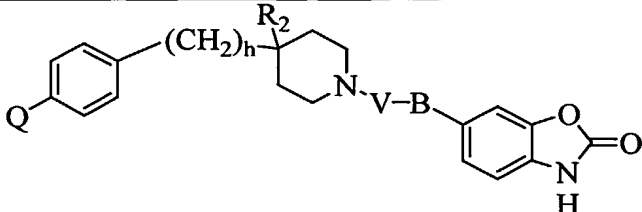
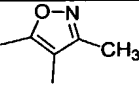
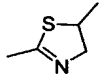
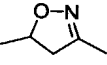
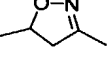
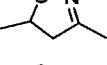
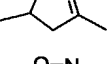
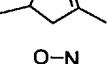
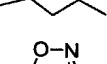
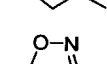
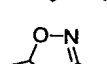
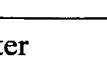
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TABLE 2

							
Example No.	B	Q	X ₁	*	IFPNR IC ₅₀ μm	FT (mg/kg)	Y
5		F	O	<i>R,S</i>	0.047	>30	O
6		F	O	NC	0.54	NT	O
7		F	S	NC	0.45	NT	S
8		H	NH	NC	0.066	NT	O
9		F	S	NC	>1	NT	O
10		H	O	NC	>1	NT	O
11		H	CH ₂	NC	>1	NT	O
12		F	O	<i>R,S</i>	0.394	NT	O
13		H	O	<i>R,S</i>	0.101	NT	O
15		F	O	NC	0.499	NT	O
21		F	O	<i>R,S</i>	0.011	NT	O
22		F	O	<i>R,S</i>	0.788	NT	O
23		F	O	<i>R,S</i>	--	NT	J

a NC means no chiral center;

b NT means not tested.

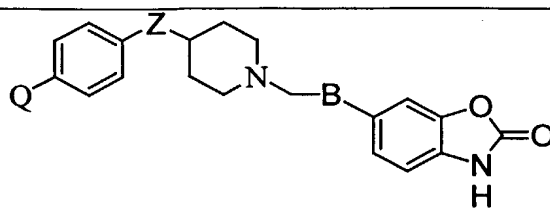
TABLE 3

							
Example No.	V	B	h	Q	R ₂	*	IFPNR IC ₅₀ (μM)
2	CH ₂		1	H	H	NC ^a	>1
14	CH ₂		1	H	H	<i>R,S</i>	0.688
17	CH ₂		1	H	OH	<i>R,S</i>	0.006
18	C=O		1	F	H	<i>R,S</i>	>1
19	CH ₂ CH ₂		1	F	H	<i>R,S</i>	0.400
20	CH ₂		1	F	OH	<i>R,S</i>	0.008
24	CH ₂		1	F	CO ₂ Et	<i>R,S</i>	--
25	CH ₂		1	F	CO ₂ H	<i>R,S</i>	--
34	CH ₂		0	F	H	<i>R,S</i>	0.280
35	CH ₂		0	H	OH	<i>R,S</i>	>1
36	CH ₂ CH ₂		0	F	H	<i>R,S</i>	>1

^a NC means no chiral center

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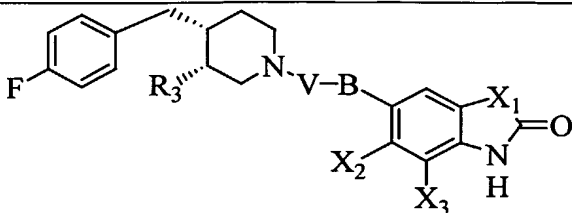
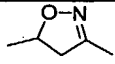
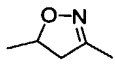
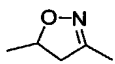
TABLE 4



Example No.	B	Z	Q	*	IFPNR IC ₅₀ (μM)
27		O	F	<i>R,S</i>	0.059
28		S	F	<i>R,S</i>	0.018
29		S=O	F	<i>R,S</i>	0.600
30		C=O	F	<i>R,S</i>	0.759
31		CH(OH)	F	<i>R,S</i>	>1
32		CMe(OH)	F	<i>R,S</i>	>1

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TABLE 5

								
Example No.	V	B	R ₃	X ₁	X ₂	X ₃	*	IFPNR IC ₅₀ (μM)
16	CH ₂		H	S	H	H	<i>R,S</i>	0.002
26	CH ₂		OH	O	H	H	<i>R,S</i>	0.023
33	CH ₂		H	O	Me	Cl	<i>R,S</i>	0.014

As shown in the above tables, compounds of the invention are potent antagonists at the NMDA receptor and orally active in vivo in models of Parkinson's disease and pain.

In addition to the oral dosing forms described above, the compounds of the invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. The following dosage forms may comprise as the active component a compound of Formula I or a pharmaceutically acceptable salt thereof.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape
5 and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax,
10 cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges
15 can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted, and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to
20 solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

25 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or,
30 synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 to 100 mg preferably 0.5 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as antagonists or as agents for the treatment of diseases, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01-mg to about 10 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, the compound being employed.

Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Examples of pharmaceutical preparations of the compounds of the invention is described below. Such preparations can be administered to a human

from one to six times a day for treatment of disease caused by over excitation of NMDA receptor channel complexes.

EXAMPLE 37

Tablet Formulation:

Ingredient	Amount (mg)
Compound of Example 1	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

The compound of Example 1, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet.

10

EXAMPLE 38

Coated Tablets:

The tablets of Example 17 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

EXAMPLE 39

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Injection vials:

The pH of a solution of 500 g of the compound of Example 1 and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the compound of Example 1.

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EXAMPLE 40

Suppositories:

A mixture of 25 g of the compound of Example 1, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each
5 suppository contains 25 mg of the compound of Example 1.

EXAMPLE 41

Solution:

A solution is prepared from 1 g of the compound of Example 1, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$, and 0.1 g benzalkonium chloride
10 in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 25 mg of the compound of Example 1.

EXAMPLE 42

15 Ointment:

500 mg of the compound of Example 1 is mixed with 99.5 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 25 mg of the compound of Example 1.

EXAMPLE 43

20 Capsules:

2 kg of the compound of Example 1 are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the invention compound.

EXAMPLE 44

25 Ampoules:

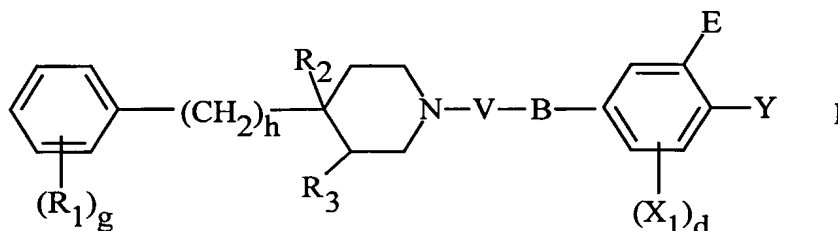
A solution of 2.5 kg of the compound of Example 1 is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into

ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg of the compound of Example 1.

- While the forms of the invention exemplified herein such as, for example, the named species of Formula IV or the recitation of treatment of pain or
- 5 Parkinson's disease constitute preferred embodiments of the invention, many other preferred embodiments are possible. It is not intended that the preferred embodiments of compounds of Formula IV, or preferred methods of use of said compounds, recited above should, in any manner, limit or restrict the invention from the full scope claimed herein.

IN THE CLAIMS:

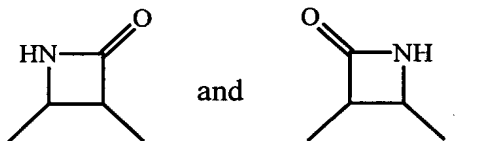
1. A compound of Formula I



and pharmaceutically acceptable salts thereof wherein:

- 5 R_1 is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkylaminoalkyl, hydroxyalkyl, (aminocarbonyl)-alkyl, (alkylthio)-alkyl, carboxyalkyl, haloalkyl, and halogen;
- g is an integer of from 0 to 3;
- 10 h is an integer of from 0 or 1;
- R_2 is hydrogen, OH, alkoxy, or substituted alkoxy;
- R_3 is hydrogen, OH, alkoxy, or substituted alkoxy;
- V is $(CH_2)_n$ or $(CH_2)_m-C=O$, wherein n is an integer of from 1 to 4, and m is an integer of from 0 to 4;
- 15 B is a 4-, 5-, or 6-membered, carbon-linked, substituted or unsubstituted, heterocyclene, containing from 1 to 3 heteroatoms, which are N, O, or S, selected from the group consisting of:

- (i) 1-aza-2-cyclobutanon-3,4-diyl of formula

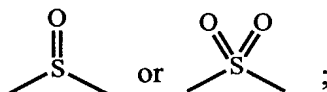


- 20 (ii) a 5-membered aromatic, nonaromatic dihydro, or nonaromatic tetrahydro diradical heterocyclic ring having carbon atoms and from 1 to 3 heteroatoms selected from N, O, and S;

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- (iii) a 5-membered oxo-substituted, nonaromatic tetrahydro, diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms selected from N, O, and S;
- (iv) a 6-membered aromatic, nonaromatic tetrahydro, or nonaromatic hexahydro diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms, which heteroatoms are nitrogen, and
- (v) a 6-membered nonaromatic oxo-substituted hexahydro diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms which are nitrogen and 0 or 1 heteroatom which is oxygen

wherein the atoms of the heterocyclene ring that are bonded to the group V and the phenyl bearing the group $(X_1)_d$ are carbon atoms, and further wherein when B is a nonaromatic heterocycle containing sulfur, said sulfur may further comprise



X_1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, aralkyl, substituted aralkyl, halogen, haloalkyl, cyano, nitro, amino, aminoalkyl, alkylaminoalkyl, hydroxyalkyl, carboxyalkyl, (aminocarbonyl)-alkyl, (alkylthio)-alkyl, or C(O)-alkyl;

d is an integer of from 0 to 2;

E is hydrogen; and

Y is OH; or

E and Y may be taken together with the phenylene to which they are attached to form a fused 9- or 10-membered bicyclic ring, containing from 0 to 3 heteroatoms in E-Y selected from N, O, and S, wherein

E is a linker group containing 2 or 3 atoms of the bicyclic

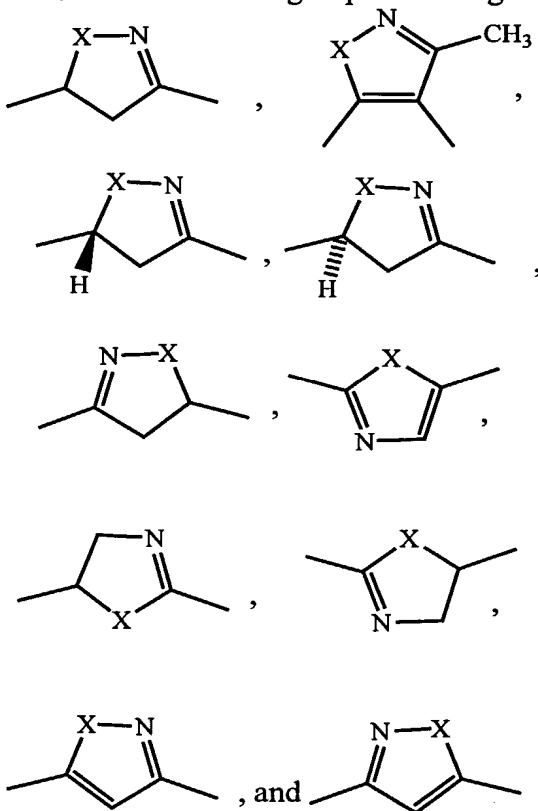
ring, and

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Y is a hydrogen bond donor group containing 1 atom of the bicyclic ring.

2. A compound according to Claim 1 wherein:

B is a heterocyclene selected from the group consisting of:



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wherein X is selected from O, S, and N-R, wherein R is hydrogen or alkyl;
X₁ is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy,

substituted alkoxy, aralkyl, halogen, haloalkyl, cyano, nitro, amino,
aminoalkyl, alkylaminoalkyl, hydroxyalkyl, carboxyalkyl,
(aminocarbonyl)-alkyl, (alkylthio)-alkyl, or C(O)CH₃, and one X₁

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is ortho to V and para to E; and

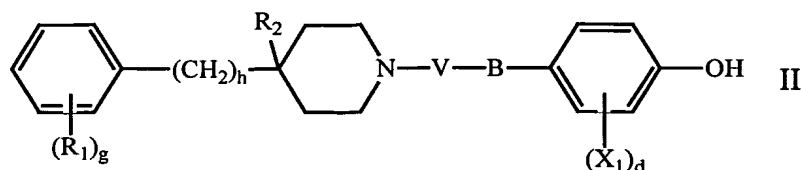
R₂ is hydrogen or OH;

V is CH₂ or C=O; and

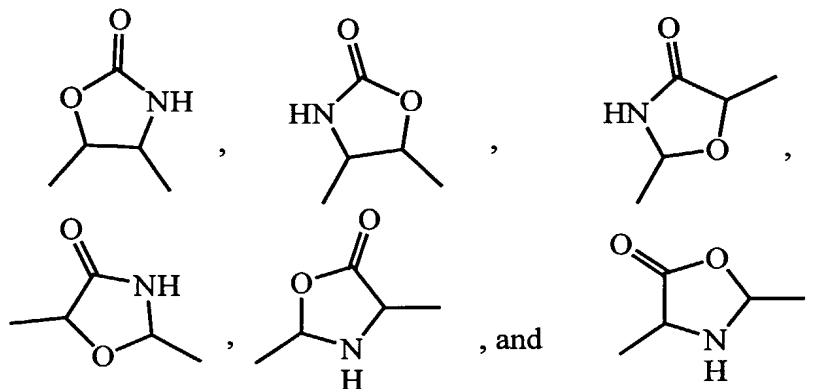
h is 1.

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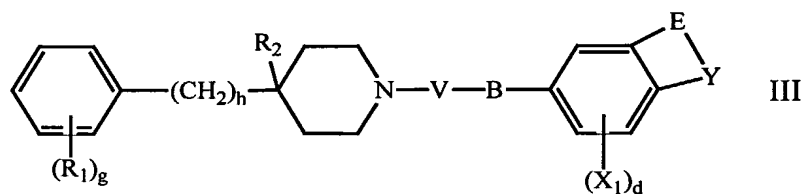
3. A compound according to Claim 1 of Formula II



and pharmaceutically acceptable salts thereof wherein when B is a 5-membered oxo-substituted, nonaromatic tetrahydro, diradical heterocyclic ring having carbon atoms and 1 or 2 heteroatoms selected from N, O, and S which is an oxazolidinone, the oxazolidinone is selected from



4. A compound according to Claim 1 of Formula III



and pharmaceutically acceptable salts thereof wherein E and Y together with the phenylene to which they are attached form a 9- or 10-membered bicyclic ring, containing from 0 to 3 heteroatoms selected from N, O, and S wherein

E is a linker group containing 2 or 3 atoms of the bicyclic ring; and

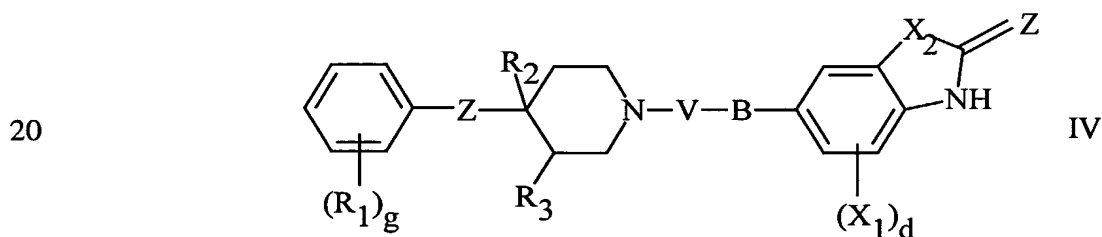
Y is a hydrogen bond donor group containing 1 atom of the bicyclic ring.

5. A compound according to Claim 4 wherein:
 Y is selected from -N(H)-, -CH(OH)-, and -N(OH)-, and
 E is selected from -CH=CH-, -CH₂-CH₂-, -CH=N-, -C(O)-CH₂-,
 -CH₂-C(O)-, -CH₂-S(O)-, -CH₂-S(O)₂-, -N=C(H)-, -N(H)-C(O)-,
 5 -O-C(O)-, -S-C(O)-, -N=N-, -CH=CH-C(H)-, -CH₂-CH₂-CH₂-,
 -CH₂-CH₂-C(O)-, -CH₂-CH₂-S(O)-, -CH₂-CH₂-S(O)₂-,
 -CH=CH-C(O)-, -N=CH-C(O)-, -O-CH₂-C(O)-, -S-CH₂-C(O)-,
 and -N(H)-C(O)-C(O)-; or
 Y is selected from =C(OH)-; and
 10 E is selected from -CH=CH-C(H)=, -C(O)-C(H)=, -C(O)-N=, -O-N=,
 -S-N=, -C(O)-N(H)-N=, -CH=N-N=, -CH=N(O)-N=, and
 -N(H)-C(O)-N=.
6. A compound according to Claim 5 wherein:
 -E-Y- is selected from the group consisting of
 15 -CH=CH-N(H)-,
 -(CH₂)₂-N(H)-,
 -CH=N-N(H)-,
 C(O)-CH₂-N(H)-,
 -CH₂-C(O)-N(H)-,
 20 -CH₂-S(O)-N(H)-,
 -CH₂-S(O)₂-N(H)-,
 -CH=CH-CH(OH)-,
 -(CH₂)₂-CH(OH)-,
 -C(O)-C(H)=C(OH)-,
 25 -C(O)-N=C(OH)-,
 -N=CH-N(H)-,
 -N(H)-C(O)-N(H)-,
 -O-C(O)-NH-,
 -S-C(O)-NH-,

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- O-N=CH(OH)-,
 -S-N=CH(OH)-,
 -N=N-N(H)-,
 -N=N-N(OH)-,
 5 -CH=CH-CH=C(OH)-,
 -(CH₂)₃-CH(OH)-,
 -(CH₂)₂-C(O)-N(H)-,
 -(CH₂)₂-S(O)-N(H)-,
 -(CH₂)₂-S(O)₂-N(H)-,
 10 -CH=CH-C(O)-N(H)-,
 -C(O)-NH-N=C(OH)-,
 -CH=N-N=C(OH)-,
 -CH=N(O)-N=C(OH)-,
 -N(H)-C(O)-N=C(OH)-,
 15 -N=CH-C(O)-NH-,
 -O-CH₂-C(O)-NH-,
 -S-CH₂-C(O)-NH-, and
 -N(H)-C(O)-C(O)-N(H)-.

7. A compound according to Claim 6 of Formula IV

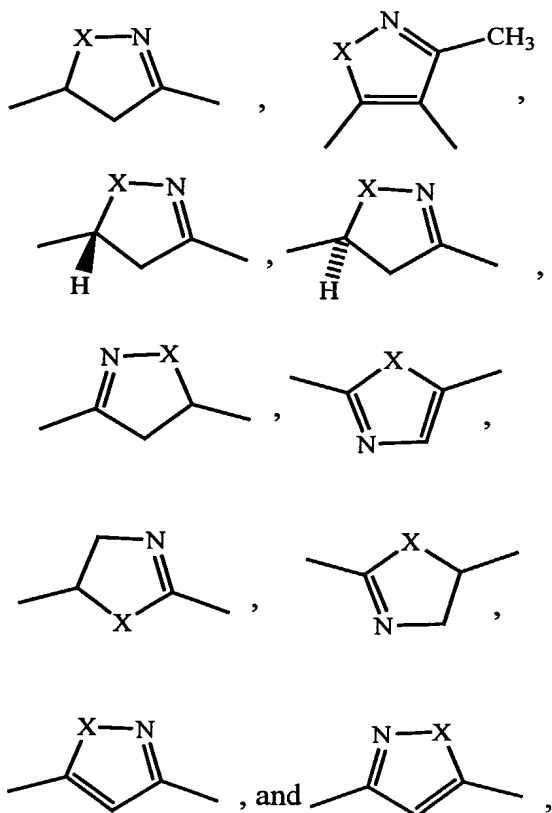


and pharmaceutically acceptable salts thereof wherein

X₂ is selected from O, S, NH, and CH₂; and

B is selected from the group consisting of:

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wherein X is selected from O, S, and N-R, wherein R is hydrogen or alkyl, and wherein Z is from O or S.

8. A compound according to Claim 4 selected from the group consisting of:
 - 5 6-[5-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one;
 - 6-[5-(4-Benzylpiperidin-1-ylmethyl)-3-methylisoxazol-4-yl]-3*H*-benzoxazol-2-one;
 - 6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-
 - 10 dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one hydrochloride;
 - (+)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-
 - dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;
 - (-)-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-
 - dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;
 - 15 6-{3-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-
 - dihydroisoxazol-5-yl}-3*H*-benzoxazol-2-one;

- 6-{2-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3*H*-benzoxazol-2-one;
- 6-{2-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]thiazol-5-yl}-3*H*-benzothiazol-2-one;
- 5 5-[2-(4-Benzylpiperidin-1-ylmethyl)thiazol-5-yl]-1,3-dihydrobenzimidazole-2-thione;
- 6-{2-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]oxazol-5-yl}-3*H*-benzothiazol-2-one;
- 10 6-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-3*H*-benzoxazol-2-one;
- 5-[2-(4-Benzylpiperidin-1-ylmethyl)oxazol-5-yl]-1,3-dihydroindol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydrothiazol-2-yl}-3*H*-benzoxazol-2-one;
- 15 6-[5-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydrothiazol-2-yl]-3*H*-benzoxazol-2-one;
- 6-[2-(4-Benzylpiperidin-1-ylmethyl)-4,5-dihydrothiazol-5-yl]-3*H*-benzoxazol-2-one;
- 20 6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]isoxazol-3-yl}-3*H*-benzoxazol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)piperidin-1-yl]methyl}-4,5-dihydroisoxazol-3-yl}-3*H*-benzothiazol-2-one;
- 6-[5-(4-Benzyl-4-hydroxypiperidin-1-ylmethyl)-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one;
- 25 6-{5-[4-(4-Fluorobenzyl)piperidine-1-carbonyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;
- 6-(5-{2-[4-(4-Fluorobenzyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one;
- 6-{5-[4-(4-Fluorobenzyl)-4-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;
- 30 6-{5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-5-methyl-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

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5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid;

5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazole-5-carboxylic acid methyl ester;

4-(4-Fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid ethyl ester;

4-(4-Fluorobenzyl)-1-[3-(2-oxo-2,3-dihydrobenzoxazol-6-yl)-4,5-dihydroisoxazol-5-ylmethyl]piperidine-4-carboxylic acid;

6-{5-[4-(4-Fluorobenzyl)-3-hydroxypiperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{5-[4-(4-Fluorophenoxy)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{5-[4-(4-Fluorophenylsulfanyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{5-[4-(4-Fluorobenzenesulfinyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-{5-[4-(4-Fluorobenzoyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-(5-{4-[(4-Fluorophenyl)hydroxymethyl]piperidin-1-ylmethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one;

4-Chloro-6-{5-[4-(4-fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-5-methyl-3*H*-benzoxazol-2-one;

-{5-[4-(4-Fluorophenyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl}-3*H*-benzoxazol-2-one;

6-[5-(4-Phenyl-4-hydroxy)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl]-3*H*-benzoxazol-2-one; and

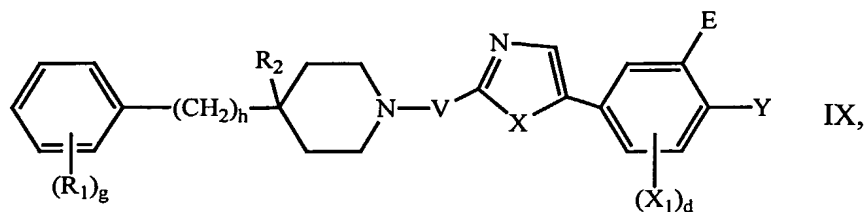
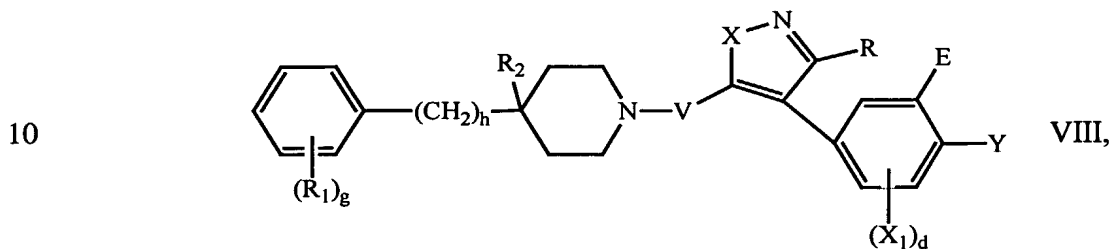
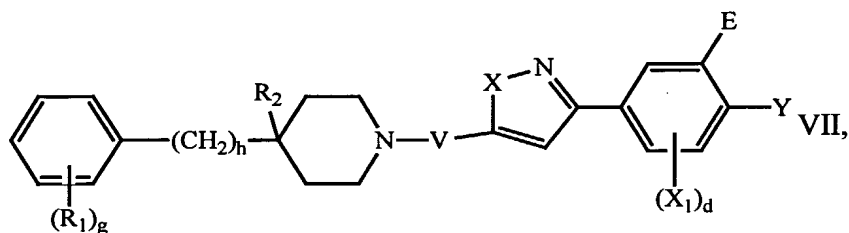
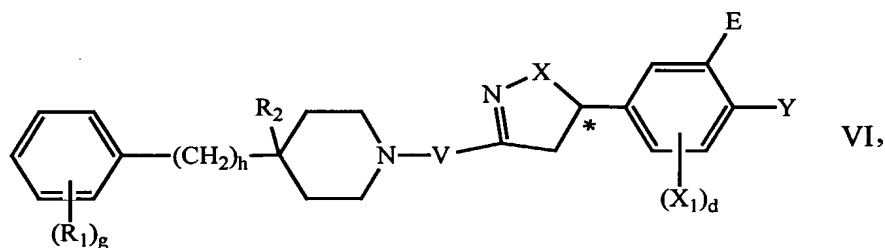
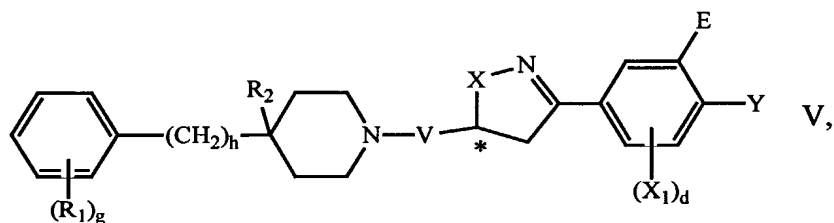
6-(5-{2-[4-(4-Fluorophenyl)piperidin-1-yl]ethyl}-4,5-dihydroisoxazol-3-yl)-3*H*-benzoxazol-2-one.

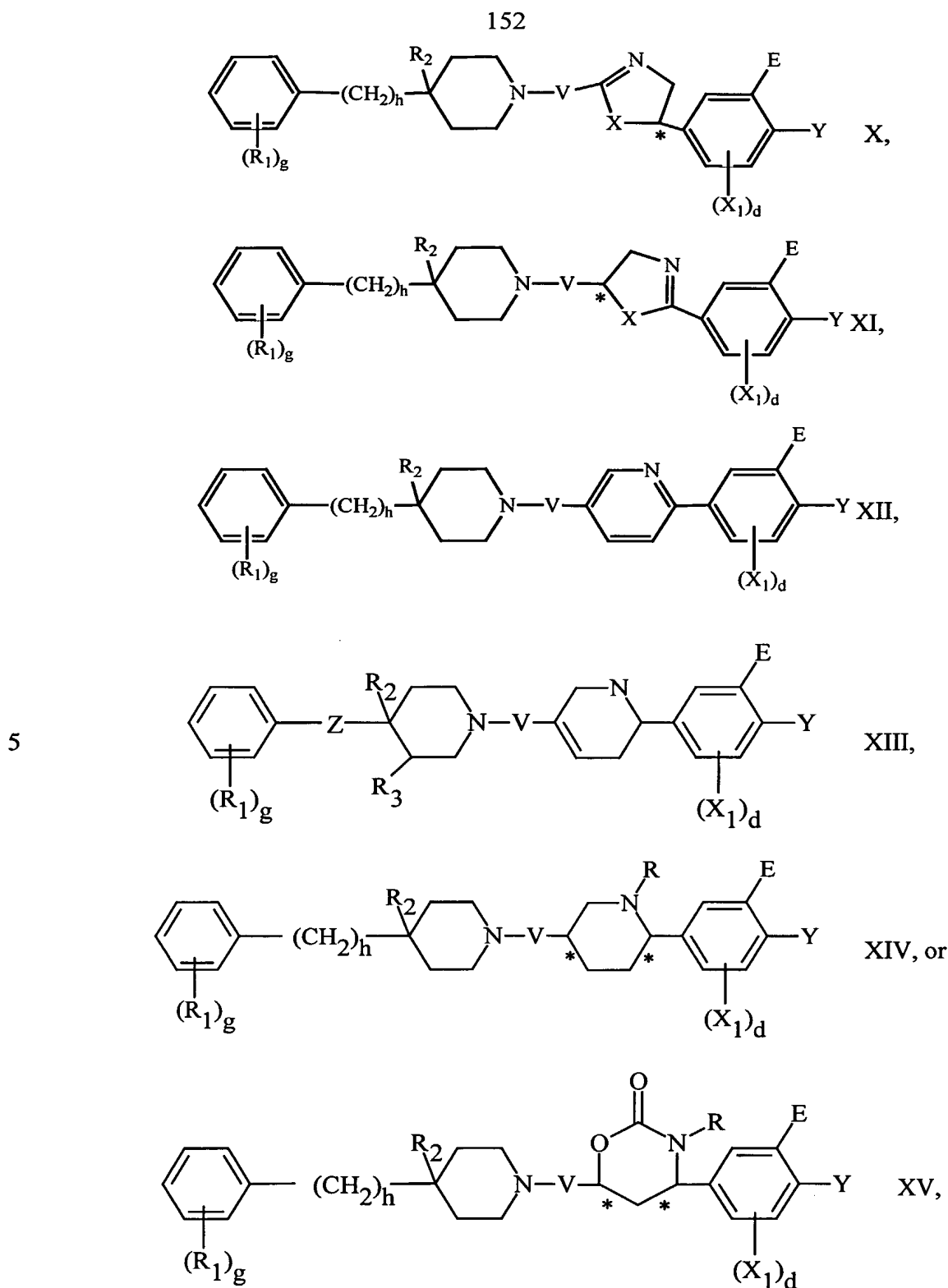
9. A compound according to Claim 4 named

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(+)-6-{5-[4-(4-Fluoro-benzyl)-piperidin-1-ylmethyl]-4,5-dihydro-isoxazol-3-yl}-3H-benzoxazol-3-one.

10. A compound according to Claim 4 named
 (-)-6-{5-[4-(4-Fluoro-benzyl)-piperidin-1-ylmethyl]-4,5-dihydro-isoxazol-3-yl}-3H-benzoxazol-3-one.
11. A compound according to Claim 1 of Formulae V,





and pharmaceutically acceptable salts thereof wherein X is O, S, or N-R, wherein R is hydrogen, alkyl, or substituted alkyl; and

* means a chiral center designated *R*, *S*, or mixtures thereof.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I-XV, or a pharmaceutically acceptable salt thereof, together with a diluent, carrier, or excipient.
13. A pharmaceutical composition according to Claim 12 comprising a therapeutically effective amount of a compound selected from the group consisting of:
- (+)-6-{5-[4-(4-Fluoro-benzyl)-piperidin-1-ylmethyl]-4,5-dihydro-isoxazol-3-yl}-3H-benzoxazol-3-one; and
- (-)-6-{5-[4-(4-Fluoro-benzyl)-piperidin-1-ylmethyl]-4,5-dihydro-isoxazol-3-yl}-3H-benzoxazol-3-one.
14. A method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal, including a human, suffering therefrom, comprising administering a compound of Formula I-XV, or a pharmaceutically acceptable salt thereof.
15. A method according to Claim 14 wherein the disorders are selected from stroke, cerebral ischemia, central nervous system disorders, depression, trauma, hypoglycemia, neurodegenerative disorders, including Parakinson's disease, anxiety, migraine headache, convulsions, aminoglycoside antibiotics-induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal, pain, including chronic pain, neuropathic pain, or surgical pain, and urinary incontinence.

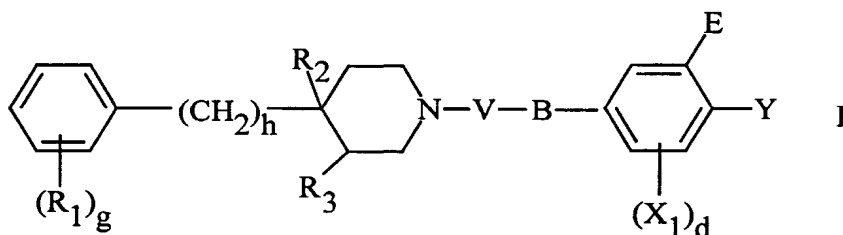
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- (71) Applicant (for all designated States except US):
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- (72) Inventors; and
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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(54) Title: PIPERIDINE DERIVATIVES AS SUBTYPE SELECTIVE N-METHYL-D-ASPARTATE ANTAGONISTS



(57) Abstract: Described are piperlines of Formula (I) and pharmaceutically acceptable salts thereof. The compounds of Formula (I) are antagonists of NMDA receptor channel complexes useful for treating cerebral vascular disorders such as, for example, stroke, cerebral ischemia, central nervous system

disorders, depression, trauma, hypoglycemia, neurodegenerative disorders, anxiety, migraine headache, convulsions, Parkinson's disease, aminoglycoside antibiotics-induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal, pain, especially chronic pain, neuropathic pain, or surgical pain, or urinary incontinence.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/02277

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/14 C07D417/14 A61K31/454 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 12924 A (MERCK PATENT GMBH ;BARTOSZYK GERD (DE); PRUECHER HELMUT (DE); GOTT) 18 March 1999 (1999-03-18) page 1, line 1 - line 11 claims 1,4-10 page 2, line 23 - line 28 ----	1-15
X	EP 0 763 535 A (MERCK PATENT GMBH) 19 March 1997 (1997-03-19) claims 1,2,4-9 ----	1-15
X	WO 00 18763 A (CHEN XI ;HE XIAO SHU (US); NEUROGEN CORP (US)) 6 April 2000 (2000-04-06) page 4, line 14 -page 5, line 18 claims 30,31 Table 1, Compounds 5 & 6 ----- -/--	1-15

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *B* document member of the same patent family

Date of the actual completion of the international search

8 July 2002

Date of mailing of the international search report

25/07/2002

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Diederer, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/02277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 16040 A (HORVATH RAYMOND F ;NEUROGEN CORP (US); PETERSON JOHN M (US); THURK) 30 May 1996 (1996-05-30) examples 16,17,18D page 6, line 7 - line 32 -----	1-15
X	PRUECHER, H. ET AL: "(5S)-3-Aryl-5-(1-piperidinylmethyl)-2-oxa- zolidinones, a new class of potential neuroleptics with a high affinity for sigma receptors" BIOORG. MED. CHEM. LETT. (1992), 2(2), 165-70 , XP008005335 Compound 8r -----	1-15
X	WO 99 50264 A (KISHIBAYASHI NOBUYUKI ;KUMAZAWA TOSHIAKI (JP); SUZUKI KOJI (JP); I) 7 October 1999 (1999-10-07) -& DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1999:640854 XP002205019 abstract -----	1,4,12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/02277

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14,15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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International Application No

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